

UDC 617.55-007.274-053.2-084:615.454.1

A.A. Kvashnina¹, M.G. Melnychenko¹, V.F. Rybalchenko²

Clinical effectiveness of sodium hyaluronate gel usage for prevention of postoperative adhesion in children

¹Odesa National Medical University, Ukraine²Shupyk National Healthcare University of Ukraine, Kyiv

Modern Pediatrics. Ukraine. (2022). 2(122): 21-26. doi 10.15574/SP.2022.122.21

For citation: Kvashnina AA, Melnychenko MG, Rybalchenko VF. (2022). Clinical effectiveness of sodium hyaluronate gel usage for prevention of postoperative adhesion in children. Modern Pediatrics. Ukraine. 2(122): 21-26. doi 10.15574/SP.2022.122.21.

It was considered expedient to study the effectiveness of intraoperative prevention of adhesion formation in children based on the results of our own experimental and clinical studies on the effectiveness of using an anti-adhesive gel based on cross-linked sodium hyaluronate.

Purpose — to evaluate clinical efficacy and safety of cross-linked sodium hyaluronate gel (SHG) usage as a barrier agent for primary prevention of postoperative peritoneal adhesions formation in children.

Materials and methods. This is a prospective, randomized, controlled, patient blinded observational study, which includes 62 children. All patients underwent laparotomy for appendicular peritonitis and were randomly divided into two equal groups. Patients from group A (n=31) received conventional surgical treatment, SHG was additionally applied in group B (n=31) before abdominal closure. Immediate and long-term effects of SHG usage were investigated to evaluate the influence on adhesions reformation. The average period of postoperative observation was 14.0±2.4 months.

Results. SHG application was associated with no increase in complications rate: duration of postoperative ileus, need in nasogastric decompression, intensive care unit state, hospital state, the incidence of surgical site infection, and need for relaparotomy did not differ significantly between compared groups. The prevalence of peritoneal adhesions at the end of in-hospital treatment differs significantly between groups according to the ultrasound data ($\chi^2=10.930$; $p=0.005$). The incidence of small bowel obstruction (SBO) developed during the follow-up period in group A (16.1%) was significantly higher than in group B (3.23%) where the anti-adhesive gel was applied ($\chi^2=4.026$; $p=0.045$).

Conclusions. Intraoperative use of SHG based on sodium hyaluronate allows reduction of postoperative adhesions formation in children without worsening the postoperative course.

The research was carried out in accordance with the principles of the Helsinki declaration. The study protocol was approved by the Local ethics committee of all participating institutions. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Key words: sodium hyaluronate, adhesions, small bowel obstruction.

Клінічна ефективність застосування гелю на основі гіалуронату натрію для профілактики післяопераційного спайкоутворення в дітей

A.A. Квашніна¹, М.Г. Мельниченко¹, В.Ф. Рибальченко²¹Одеський національний медичний університет, Україна²Національний університет охорони здоров'я України імені П.Л. Шупика, м. Київ

Вивчення ефективності інтраопераційної профілактики спайкового процесу в дітей визнано доцільним на підставі результатів власних експериментальних і клінічних досліджень ефективності застосування протиспайкового гелю на основі полімеризованого гіалуронату натрію.

Мета — оцінити клінічну ефективність і безпечність застосування гелю на основі гіалуронату натрію як бар'єрного засобу для первинної профілактики післяопераційних спайок очеревини в дітей.

Матеріали та методи. Проведено проспективне, рандомізоване, контрольоване, сліпе обсерваційне дослідження за участю 62 дітей. Усім пацієнтам виконано лапаротомію з приводу апендикулярного перитоніту. Пацієнти групи А (n=31) отримували звичайне хірургічне лікування, у групі В (n=31) перед закриттям живота додатково застосовували антиадгезивний гель (ААГ). Досліджено безпосередні та віддалені результати застосування ААГ, щоб оцінити вплив на реформування спайок. Середній термін післяопераційного спостереження становив 14,0±2,4 місяця.

Результати. Застосування ААГ не пов'язане з підвищенням частоти ускладнень: тривалість післяопераційної спайкової кишкової непрохідності, потреба в назогастральній декомпресії, тривалість надходження до стаціонару, частота інфікування місця хірургічного втручання та потреба в релaparотомії суттєво не різнилися між групами порівняння. Поширеність спайок очеревини наприкінці стаціонарного лікування за даними ультразвукового дослідження суттєво різнилася між групами ($\chi^2=10,930$; $p=0,005$). Захворюваність на спайкову кишкову непрохідність, що розвинулася протягом періоду спостереження, у групі А (16,1%) була значно вищою, ніж у групі В (3,23%), в якій застосовували ААГ ($\chi^2=4,026$; $p=0,045$).

Висновки. Інтраопераційне застосування ААГ на основі гіалуронату натрію дає змогу зменшити утворення післяопераційних перитонеальних спайок у дітей без погіршення післяопераційного перебігу.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом усіх зазначених у роботі установ. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: гіалуронат натрію, спайки, тонкокишкова непрохідність.

Introduction

Postoperative peritoneal adhesions (PPA) remain a common and unpleasant sequelae of majority of interventions in abdominal and pelvic surgery despite minimally invasive techniques implementation. Main clinically significant manifestation is adhesive small bowel obstruction (ASBO), but PPAs also lead to the infertility, chronic abdominal and pelvic pain and generally to the patient's life quality impairment. Surgical treatment of ASBO takes about 20% of all emergency laparotomies, with a mortality close to 3% [1,2,7].

In pediatric practice, on an average about 5% of patients require inpatient treatment for postoperative ASBO. After interventions in the small intestine, this complication develops most often – in every 10 children. Higher rate of ASBO after interventions in the neonatal period should be noted (8–12%) with up to 15% after malrotation correction [3,10], which also affirms the relevance of this problem in pediatric surgery.

Taking into account the effectiveness of barrier anti-adhesion agents, according to research and clinical recommendations [5,8,9,11], and based on the results of our own experimental and clinical studies about the effectiveness of anti-adhesive gel based on cross-linked sodium hyaluronate (SHG) [6], it was considered expedient to investigate the effect of the developed method of intraoperative prevention of postoperative adhesions formation in children. Also, there is a lack of information about the safety of barrier agent's usage in case of inflammation and intraabdominal infection.

The study protocol was approved by the Ethics committee of Odesa national medical university. Informative consent for participation was obtained from legal representatives of children included in the trial in all cases.

Purpose of the study – to evaluate clinical efficacy and safety of cross-linked SHG usage as a barrier agent for primary prevention of

postoperative peritoneal adhesions formation in children.

Materials and methods

This is a prospective, randomized, controlled, patient blinded observational study. Study groups included 62 children aged 3–16 years, who were treated at the Odesa Regional Children's Clinical Hospital (Ukraine) for appendicular peritonitis (AP) during the years 2015–2019. The main study group (A) and the control comparison group (B) were equal in number (n=31), randomized by gender, age, type of peritonitis, features of clinical course, and surgical approach (Table 1). Statistical significance in the difference between the mean values was determined using Student's t-test and Pearson's test χ^2 . The difference was considered statistically significant at p-value ≤ 0.05 .

The criteria for exclusion from the study groups were the following: severe peritonitis with programmed relaparotomy; the presence of intestinal anastomoses (taking into consideration the ambiguous data on the effect of barrier anti-adhesive agents on the intestinal sutures healing); the age of the child under one year (due to significant anatomical and physiological features and differences in treatment standards, which makes the comparison incorrect).

Children of both groups received treatment according to national and international recommendations and clinical protocols [3,10], depending on their general condition and intraoperative picture. In all cases, laparotomy was performed, more often a midline laparotomy (48; 77.4%). Surgical treatment included appendectomy, drainage of any intraperitoneal purulent collections, peritoneal lavage, and drainage. Normal saline was used for lavage up to «clean water».

During the operation, after the source control and lavage of the peritoneal cavity, in the group A, SHG with the active agent concentration of 10 mg/ml was applied on areas of visceral and

Characteristics of the clinical groups (p>0.05)

Table 1

Sign		Group A, n=31	Group B, n=31
Gender	Boys	14 (45.2%)	16 (51.6%)
	Girls	17 (54.8%)	15 (48.4%)
Age, years old		11.0±4.1	10.8±8.2
Duration of disease, hours		36.6±27.4	37.2±27.3
Type of peritonitis	Local	11 (35.5%)	11 (35.5%)
	Appendicular abscess	8 (25.8%)	7 (22.6%)
	Diffuse	12 (38.7%)	13 (41.9%)
Location of appendix	Medial	20 (64.5%)	22 (71.0%)
	Pelvic	4 (12.9%)	7 (22.6%)
	Retrocecal	7 (22.6%)	5 (16.1%)
Period of follow-up study, months		14±2.4	14±4.4

parietal peritoneum damage before abdominal closure [6]. Gels with a lower concentration have a lower viscosity and do not stay in place for sufficient time to prevent adhesions. In the group B, only lavage was performed intraoperatively, SHG was not used. Abdominal drainage was used according to the indications, in most cases, one PVC-tubular drainage was inserted into the Douglas pouch (52; 80.7%).

During the postoperative period, treatment of all children was treated according to the generally accepted principles. Efficacy and safety of the intraoperative prevention method were assessed by dynamics of the postoperative course during in-patient treatment based on a daily physical assessment, monitoring of residual volume with Nasogastric Tube (NGT), the term of peristalsis (auscultation and sonographic assessment) and spontaneous bowel movement restoration, the term of enteral nutrition beginning, transfer of the child from the intensive care unit (ICU), dynamics of laboratory tests, the occurrence of complications, term of hospital stay.

The risk of postoperative complications, including intra-abdominal complications, surgical site infection, and disorders of another organ's systems was also determined. Immediate preventive efficacy of the proposed technique in children with AP was evaluated after completion of inpatient treatment as «good», «acceptable» and «adverse» results using clinical and sonographic criteria.

The main criterion of long-term efficacy was the incidence of adhesive small bowel obstruction (SBO) during a follow-up period in children of studied groups.

Results

The evaluation of the immediate results of the SHG use was carried out during the period of the child's stay in the hospital. The data presented in Table 2 demonstrate that the use of SHG has no negative impact on the postoperative period. In contrast, the considered signs differed little between the comparison groups, and the restoration of peristalsis and spontaneous bowel movement was slightly earlier in children of group A.

Comparative analysis of hemograms in both groups did not differ significantly, except for C-reactive protein. Moreover, a statistically significant protective effect of SHG on the duration of systemic inflammation response (SIRS) in children with AP has been shown: in children of group A it was 2.9 ± 1.5 days as compared with 3.8 ± 1.7 in children of group B.

When analyzing the frequency and structure of postoperative complications (Table 3), it was determined that the intraoperative use of SHG does not increase the risk of complications.

In particular, the total number of postoperative complications was the same in both groups and amounted to 9 cases (29.0%). Intra-abdominal complications were observed in 3 (9.7%) patients

Table 2

Dynamics of clinical and laboratory signs at the early postoperative period

Sign	Group A	Group B	Tcr/ χ^2	p	
Duration of stay in the ICU-department, day	5.8±1.9	5.1±1.4	1.5	>0.05	
NGT removal, day	2.5±1.1	2.1±1.3	1.1	>0.05	
Peristalsis renovation, day	2.4±0.9	2.6±1.3	0.5	>0.05	
The onset if enteral feeding, day	4.1±1.4	4.0±1.4	0.1	>0.05	
Spontaneous bowel movement, day	2.9±1.0	3.3±1.1	1.6	>0.05	
Terms of SIRS removal, day	2.9±1.5	3.8±1.7	2.2	<0.05	
C-reactive protein (2 nd day), mg/l	131.2±55.0	122.5±49.3	0.1	>0.05	
WBC-count in peripheral blood, G/l	1 st day	12.3±5.9	11.2±4.5	0.9	>0.05
	3 rd day	11.4±4.6	11.2±4.5	0	>0.05
	5 th day	12.0±4.9	11.8±5.3	0.2	>0.05
Relaparotomy, abs.	4/31	3/31	0.2	>0.05	
Term of hospitalization, day	16.4±4.9	15.7±2.7	0.8	>0.05	

Table 3

The structure of postoperative complications

Complications	Group A, n=31		Group B, n=31		χ^2	p
	abs.	%	abs.	%		
Postoperative surgical site infection	2	6.5	2	6.5	–	–
Other organs complications	3	9.7	2	6.5	0.22	>0.05
Intra-abdominal inflammation	3	9.7	5	16.1	0.13	>0.05
Early adhesive small bowel obstruction	1	3.2	3	9.7	1.069	0.302
Relaparotomy	4	12.9	3	9.7	0.16	>0.05
Total	9	29.0	9	29.0	–	–

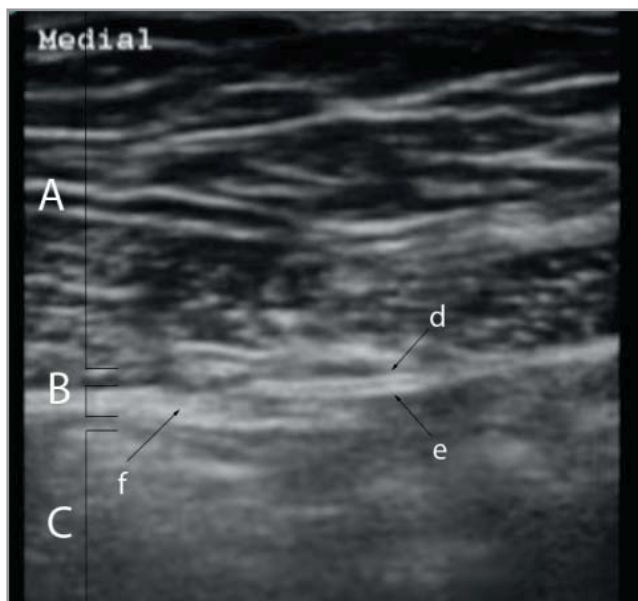


Fig. 1. Sonographic changes of fascia and peritoneum complex and adhesions attachment (the transverse section in middle epigastric region): A — abdominal wall structures; B — fascia and peritoneum complex; C — viscera; arrow d — the transverse abdominal fascia; e — the parietal peritoneum; f — FPC hypotrophy in place of adhesion attachment

of group A, of which relaparotomy was performed in all cases (interloop abscesses were detected in 2 (6.5%) cases, purulent omentitis — in 1 (3.2%) case). In group B, intra-abdominal inflammato-

ry complications developed in 5 (16.1%) patients, which was 1.5 times higher than group A (postoperative abdominal infiltrates took place in 2 (6.5%) cases, intra-abdominal abscesses — in 3 (9.7%) cases.

Moreover, SHG-based intraoperative prevention of primary adhesions in children with AP 3 times reduced the number of early adhesive SBO between patients of the study groups: among patients of group A in 3.2% of cases, in patients of group B — in 9.7%. Most of the relaparotomies was performed during the second postoperative week, SHG residues in the abdominal cavity during the intervention was not detected.

To assess the anti-adhesive effect of SHG, all children before discharge from the hospital underwent a transabdominal ultrasound which is a reliable noninvasive method of visceroparietal adhesions detection [4]. 9 anatomical areas of the abdominal wall were scanned for visceral sliding and assessing anatomy of the fascia and peritoneum complex (FPC). Visceral sliding is determined by dynamic ultrasound, using a linear transducer by recording the movement of intestinal loops relative to the abdominal wall during the patient's respiratory movements, or by using a transducer, in cases where the patient does not follow instructions. This is an easy and reliable method of revealing fixed intestinal loops, which is not

Ultrasound monitoring of treatment results in patients

Table 4

Sign	Group A		Group B		χ^2	p
	Abs.	%	Abs.	%		
Visceral sliding restriction in the scar area	8	25.8	17	54.8	5.429	0.020
Viscero-parietal adhesions in 1 anatomic area	9	29.0	7	22.6	0.076	0.783
Viscero-parietal adhesions in ≥ 2 anatomic areas	2	6.5	13	41.9	10.641	0.002
Viscero-visceral adhesions	1	3.2	3	9.7	1.069	0.302
Pelvic adhesions (girls)	4/17	23.5	7/15	46.7	1.891	0.170
Absence of peritoneal adhesions	20	64.5	11	38.7	4.133	0.043

Clinical criteria for evaluating the immediate results of treatment of children

Table 5

Criterion	Results in points		
	good (0)	acceptable (1)	adverse (2)
Duration of hospitalization	up to 15 days	15–20 days	over 20 days
Complication of postoperation period	no	no relaparotomy	relaparotomy
Abdominal pain	no	mild intensity	expressed
Abdominal distention	no	mild intensity	expressed
Dyspeptic signs	no	occasional disorders	regular disorders
Defecation	regular	occasional disorders	regular disorders
Pain at extension	no	no	present
US-signs of peritoneal adhesions	no	moderate	expressed

able to change their position in more than 1 cm. Disturbances of FPC are more sensitive criteria for visceroparietal adhesions detection. It is based on the visualization of transverse fascia and parietal peritoneum as separate hyperechogenic lines. In areas of adhesion attachment, these structures are not visualized [4]. Typical sonographic findings are compared in Figure 1, though they depend on the individual and anatomical zone.

Additionally, visceral sliding in the area of the postoperative scar and visualization of viscerovisceral adhesions were evaluated. Ultrasound of the pelvic organs in girls was performed with a determination of the condition and position of the reproductive organs and signs of pelvic adhesions. Generally, the ultrasound picture of the intra-abdominal adhesion process was regarded as absent, moderate (the presence of ultrasound signs of adhesions in one anatomical area), or expressed (in two areas or more).

The results of the control ultrasound among the examined patients are shown in Table 4.

According to the data, the presence, severity, and prevalence of intra-abdominal adhesions in children of group A were significantly lower as compared with patients in group B. In particular, the number of patients without ultrasound signs of peritoneal adhesions was significantly higher in group A – 20 (64.5%), the number of such patients in group B was only 11 (38.7%). Among patients in group A, visceroparietal adhesions were detected mostly in 1 anatomic region. The presence of adhesions in more than 1 anatomic area was found only in 6.5% of patients in group A, while in group B this kind of finding was in 41.9% patients. The general assessment of ultrasound signs of adhesion formation is illustrated in Figure 2.

As clinical criteria for assessing the effectiveness of immediate results of prevention of primary adhesions in children with AP, we used the subjective and objective signs presented in Table 5.

The result of treatment according to these criteria was considered as «good» with a total value of 0–1 point, «acceptable» – 2–4 points, «adverse» – 5–8 points. The comparative analysis of the results is illustrated in Figure 3.

The diagram illustrates that the «good» immediate result was obtained twice as often in patients of group A – in 74.2%, while in patients of group B the «good» result was only in 38.7% of cases. In children of group A, an «adverse» immediate result was noted only in 6.5%, while in children of group B an «adverse» immediate result was observed in al-

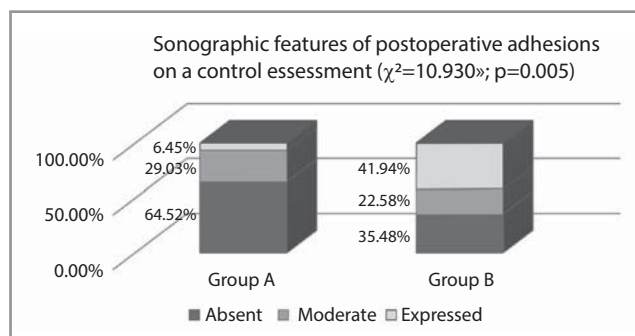


Fig. 2. Prevalence of postoperative adhesions on the control sonographic assessment

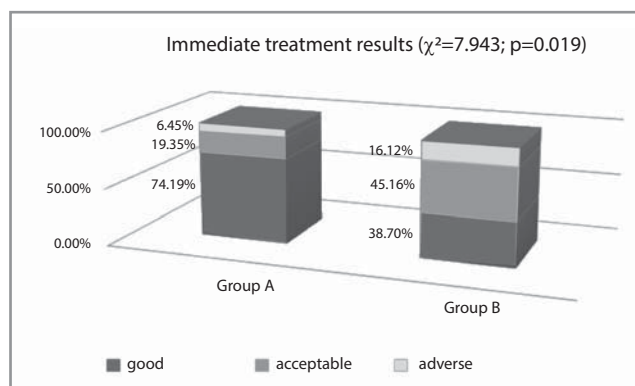


Fig. 3. Immediate clinical results of treatment of patients of the studied groups

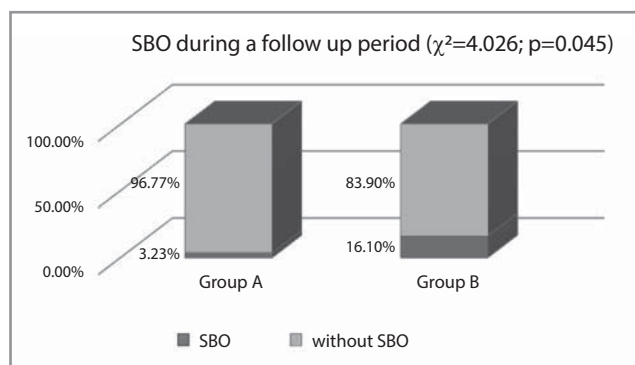


Fig. 4. Cases of late adhesive SBO in patients of the studied groups

most 16.1% of cases. The value of χ^2 is 7.943 with a critical value of 5.991 for a significance level of $p=0.05$.

Discussion

Summarizing the above said, we consider that intraoperative use of SHG based on polymerized sodium hyaluronate with an active agent concentration of 10 mg/ml, as a barrier to the prevention of primary postoperative adhesions, is safe, because it does not increase complications rate and relaparotomy, does not prolong the postoperative ileus and does not affect the hospitalization term. Postoperative monitoring did not differ statistically significantly between patient groups, but there

was an effect on faster SIRS elimination at the postoperative period.

We investigated long-term results in the studied children at the average observation period of 14 ± 2.4 months. The main criterion for evaluating the results was the reduction in the number of hospitalizations and the need for surgical treatment for adhesive SBO. The analysis results are illustrated in Figure 4.

The number of hospitalizations for adhesive SBO in group A, where intraoperative prevention of adhesions has been done, significantly less (3.2% of cases), as compared with 16.1% in patients of group B. All cases of adhesive SBO in group A required surgical treatment whereas in group B the need in laparotomy for late adhesive SBO occurred in 9.7% of cases. The difference in surgical treatment requirements during the period of observation didn't differ significantly ($\chi^2=1.069$; $p=0.302$).

Conclusions

Prevention of primary postoperative adhesion formation in the complex treatment of children with AP by intraoperative use of SHG based on cross-linked sodium hyaluronate with an active agent concentration of 10 mg/ml is safe and effective.

The expressed adhesion process by ultrasound signs was recorded only in 6.5% of patients in

group A, while in group B this picture was seen in 41.9% of cases.

The number of hospitalizations for late adhesive SBO after the use of SHG in children was significantly lower ($\chi^2=4.026$; $p=0.045$) in group A.

Intraoperative use of SHG based on sodium hyaluronate allows reduction of postoperative adhesions formation in children without worsening the postoperative course. The developed technique should be investigated in bigger studies because seems to be an easy and feasible way to reduce the incidence of adhesive intestinal obstruction in children.

Prospects for further research

In our research effectiveness and safety of AAG as a feasible method of postoperative adhesions prevention was proven, however before its recommendation for widespread clinical use further research including larger groups of children is necessary to collect more data for persuasive conclusions. We still provide monitoring of long-term efficacy of the method as there is a lifelong risk of adhesion-related sequela, therefore collected data can contribute to the results of the study. Moreover, investigation of this preventive method in different surgical pathology has a big potential in the improvement of pediatric surgical care.

No conflict of interests was declared by the authors.

REFERENCES/ЛІТЕРАТУРА

1. Capella—Monsonis H, Kearns S, Kelly J, Zeugolis DI. (2019). Battling adhesions: from understanding to prevention. BMC biomedical engineering. 1: 5. doi: 10.1186/s42490-019-0005-0.
2. Catena F, Di Saverio S, Coccolini F, Ansaloni L et al. (2016). Adhesive small bowel adhesions obstruction: Evolutions in diagnosis, management and prevention. World journal of gastrointestinal surgery. 8 (3): 222–231. doi: 10.4240/wjgs.v8.i3.222.
3. Di Saverio S, Podda M, De Simone B, Ceresoli M et al. (2020). Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World journal of emergency surgery: WJES. 15 (1): 27. doi: 10.1186/s13017-020-00306-3.
4. Gerner—Rasmussen J, Donatsky AM, Bjerrum F. (2019). The role of non-invasive imaging techniques in detecting intra-abdominal adhesions: a systematic review. Langenbecks Arch Surg: 653–661. doi: 10.1007/s00423-018-1732-8.
5. Isa MA, Bodnar OB. (2017). Hyaluronic acid solution as a treatment of adhesive intestinal obstruction in children — A positive effect: PS230. Porto biomedical journal. 2 (5): 246. doi: 10.1016/j.pbj.2017.07.164.
6. Melnichenko M, Sytnikova V, Kvashnina A. (2018). The effect of anti-adhesive gels based on sodium hyaluronate on the formation of intraperitoneal adhesions in the experiment. Klin. Khirurgiia. 85 (12): 64–67. [Мельниченко МГ, Ситнікова ВО, Квашніна АА. (2018). Вплив антиадгезивних гелів на основі гіалуронату натрію на формування інтраперитонеальних спайок в експерименті. Клін. хірургія. 85 (12): 64–67]. doi: 10.26779/2522-1396.2018.12.64.
7. Miyake H, Seo S, Pierro A. (2018). Laparoscopy or laparotomy for adhesive bowel obstruction in children: a systematic review and meta-analysis. Pediatric surgery international. 34 (2): 177–182. doi: 10.1007/s00383-017-4186-0.
8. Schmitt VH, Mamilos A, Schmitt C, Neitzer—Planck C et al. (2018). Tissue response to five commercially available peritoneal adhesion barriers—A systematic histological evaluation. Journal of biomedical materials research. Part B. Applied biomaterials. 106 (2): 598–609. doi: 10.1002/jbm.b.33835.
9. Sultana T, Gwon JG, Lee BT. (2020). Thermal stimuli-responsive hyaluronic acid loaded cellulose based physical hydrogel for post-surgical de novo peritoneal adhesion prevention. Materials science & engineering. C, Materials for biological applications. 110: 110661. doi: 10.1016/j.msec.2020.110661.
10. Ten Broek R, Krielen P, Di Saverio S, Coccolini F et al. (2018). Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World journal of emergency surgery: WJES. 13: 24. doi: 10.1186/s13017-018-0185-2.
11. Wu W, Cheng R, das Neves J, Tang J et al. (2017). Advances in biomaterials for preventing tissue adhesion. Journal of controlled release: official journal of the Controlled Release Society. 261: 318–336. doi: 10.1016/j.jconrel.2017.06.020.

Відомості про авторів:

Квашніна Анастасія Андріївна — магістр медицини, асистент каф. дитячої хірургії Одеського НМУ. Адреса: м. Одеса, Валіховський провул., 2. <https://orcid.org/0000-0003-3704-2047>.

Мельниченко Марина Георгіївна — д.мед.н., проф., проф. каф. дитячої хірургії Одеського НМУ. Адреса: м. Одеса, Валіховський провул., 2. <https://orcid.org/0000-0001-9066-4801>.

Рибальченко Василь Федорович — д.мед.н., проф., проф. каф. дитячої хірургії НУОЗ України імені П.Л. Шупика. Адреса: м. Київ, вул. Дорогожицька, 9. <https://orcid.org/0000-0002-1872-6948>.

Стаття надійшла до редакції 10.11.2021 р., прийнята до друку 06.03.2022 р.