

## Prognosis of the Development of Abdominal Adhesions After Appendectomy

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Received: February 25, 2022

Published: March 11, 2022

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### Abstract

A comparison of several parameters in 53 operated patients with abdominal adhesions and 53 patients without abdominal adhesions was made to elaborate prognostic criteria for the development of abdominal adhesions in patients after appendectomy. Considering the informative value of the criteria including obesity, acetylation status, propensity for excessive scarring, appendix location, allergy, gastrointestinal disorders, absence of connective tissue dysplasia syndrome (CTDS), they shall be considered risk factors favoring the development of postoperative abdominal adhesions in patients with acute appendicitis (AA). Results of surgical treatment in 360 patients with acute appendicitis have been presented. Group 1 (Control 1) included 120 patients who received standard treatment. Group 2 (Control 2) comprised 120 patients who underwent laparoscopic appendectomy. Group 3 (Main) included 120 patients whom laparotomy appendectomy as *fast-track surgery* was offered. Anti-adhesion therapy in high-risk patients allowed to reduce potential development of abdominal adhesions by 3.9 times, i.e. from 34.5% to 8.8%. A multimodality approach to treat patients with acute appendicitis resulted in a 3.23-time reduction of postoperative adhesion formation process compared to open appendectomy, and a 1.75-time reduction for laparoscopic approach.

**Keywords:** Acute Appendicitis; Prognosis; Prevention; Abdominal Adhesions

### Relevance

In the last decades, there has been a trend towards reduction of AA morbidity, however, appendectomy remains one of the most common surgeries in the emergency surgery making 20 to 85% among all urgent surgeries based on literature sources [1,3,5]. The quantity of unjustified appendectomies, as some authors say, is between 30 and 38.7%, while it is 6.6% for laparoscopy [2,6]. At the same time, undue delay of operation is associated with postoperative complications in 8-10% of cases making 40% for the destructive forms of AA [4,7]. Prognosis for the development of postoperative abdominal adhesions will facilitate outlining the group of patients requiring anti-adhesion treatment. There have been yet

no effective means to control pathological adhesion formation with only sparse reports on how to prevent abdominal adhesions following the appendectomy, but they are fragmented and unstructured.

### Objective

Improved therapeutic results in patients with acute appendicitis by prognosing and prevention of abdominal adhesions after the appendectomy.

### Material and Methods

The present work describes the results of examination and treatment obtained from 360 patients with various clinical forms of

acute appendicitis. The exclusion criteria were acute appendicitis with widespread peritonitis, dense appendicular lump and counterindications for laparoscopy. Some parameters were compared in 53 operated patients with abdominal adhesions and 53 patients without abdominal adhesions to elaborate prognostic criteria of abdominal adhesions following the appendectomy. Based on the examination methods, treatment modality and surgical treatment patients with AA were distributed into three groups. Group 1 (Control 1) included 120 patients who received standard treatment. Group 2 (Control 2) comprised 120 patients who underwent laparoscopic appendectomy. Group 3 (Main) included 120 patients who received laparotomy appendectomy as fast-track surgery. The information about the upcoming surgery, operation results, specificities of post-operative period, and fast-track surgery advantages was communicated to the patients; 10 to 15 minutes before the operation, skin in the surgical field was exposed to UV radiation; 30 minutes before the operation, endolymphatic antibiotic prophylaxis was offered including 1.0 i.v. cefazoline, 1.0 cefazoline + 300 mg metronidazole + 4 ml 2% lidocaine solution subcutaneously into the dorsum of foot; intraoperative anesthesia was accomplished by total i.v. anesthesia: 1% propofol solution 4-8 mg/h combined with 5% ketamine solution 3-4 mg/kg body mass; elderly patients and patients with severe cardiovascular comorbidities opted for spinal anesthesia (15-20 mg 0.5% naropin solution); surgical access was made with Surgitron electric knife; appendix stump was immersed into purse-string suture without preliminary dressing; abdominal drainage was not performed; for post-operative wound closure: parietal peritoneum was not sutured; aponeurosis was sutured with Prolene monofilament; before suturing the subcutaneous tissue and the skin the injury was conditioned with 0.5% chlorhexidine and 3% hydrogen peroxide for 3 minutes; intradermic suture with Prolene monofilament does not disturb blood flow along the wound margins and prevents permeability of the suture material for infection; in the postoperative period, opioid analgesic agents were rejected and anesthesia included i.v. infusion or intramuscular administration of 5% ketoprofen 100 mg x 2 times daily; in case of analgesic inefficiency, a single i.m. administration of 100 mg 5% tramadol was added; within 6 hours after the surgery, early enteral feeding, early bowel movement stimulation and early activation of patients were offered, i.e. 6 hours out of bed given adequate analgesia within 1 day after the surgery. During the examination, patients underwent clinical, laboratory (acetylation profile, immunosorbent assay to detect propensity for abdominal adhesions,

Quetelet index, etc.), instrumental (US, CT, laparoscopy) and histology examinations. Clinical data registration, statistical processing and graphic descriptions were made using Biostat, SPSS 17.0. and EpiInfo and Microsoft Office package. Differences between the means compared were assessed using standard deviations and considered reliable by Student's test  $p > 0.05$  and Fisher's criterion  $p > 0.05$ .

## Examination Results

Several parameters in 53 operated patients were analyzed to define prognostic criteria for the development of abdominal adhesions in patients after the appendectomy. Abdominal adhesion formation process was detected in 36 (67.9%) subjects by ultrasound, 11 (20.8%) by computerized tomography and 6 (11.3%) subjects during surgeries due to other abdominal pathology. A control group included 53 subjects who had no abdominal adhesions after the surgery due to acute appendicitis.

Of 106 patients of both groups, 46 patients (43.4%) had body mass index (BMI) between 18.5 and 24.9. Excessive body mass was recorded in 22 (20.8%) patients. The IIa and IIb degree obesity was found in 30 (28.3%) patients who underwent appendectomy. In patients with poor or normal body mass, abdominal adhesion formation process postoperatively was seen 22.6% less frequently compared to patients who had no abdominal adhesions. Nineteen (35.8%) patients with abdominal adhesions showed IIa to III-degree obesity whereas this estimate was much lower in the comparison group making 11 (20.8%) patients.

Time from the onset of AA before the admission to the hospital differed varying between several hours to more than 1 day. Of 53 patients with abdominal adhesions, 20 individuals (37.8%) were admitted in the first 6 hours from the onset of abdominal pains; 14 individuals (26.4%) between 7 to 12 hours; 13 (24.5%) individuals between 13 and 24 hours; and 6 operated subjects (11.3%) more than 24 hours. Interestingly, the greater the late admission rate of outpatient patients was, the more frequent the diagnosis of gangrenous AA was: within 6 h for 10.0%; 7 to 12 h for 21.4%; 13 to 24 h for 30.7% and after a 24-h period for 50.0% of cases. The dynamics is inverse when acute phlegmonous appendicitis is verified: within 6 h for 74.5%; 7 to 12 h for 67.6%; 13 to 24 h for 57.1% and after a 24-h period for 54.5% of cases. Variations in diagnosing catarrhal AA at different time periods are not reliable ( $P < 0.05$ ).

Within the first 6 hours from the onset, medical help was sought by patients who were later diagnosed with: catarrhal AA - 5 (9.4%) patients, phlegmonous - 15 (28.3%) and gangrenous AA - 1 (1.9%) patient. In the first 12 hours from the first symptoms prior to admission, 33 (62.3%) individuals sought medical care. Catarrhal appendicitis was confirmed in 3 (5.7%) patients, phlegmonous in 10 (18.9%) and gangrenous in 3 (5.7%) patients. A total of 48 (90.6%) patients were admitted with the age of the onset within 24 hours: 10 (18.9%) with catarrhal AA, 31 (58.5%) with phlegmonous and 7 (13.2%) with gangrenous. Five (9.4%) patients sought medical assistance extraordinarily late, of which 2 (3.8%) showed changes in the appendix estimated as phlegmonous, and 3 (5.7%) - as gangrenous AA. These data suggest there is no statistically significant correlation between intra-abdominal adhesions and the pattern of changes in the vermiform appendix ( $P < 0.05$ ).

Among patients with AA who underwent appendectomy but had no adhesions in the abdominal cavity were patients aged 20-29 years old - 19 (35.8%). The prevalence was nearly similar in patients 30 to 39 and 40 to 49 years of age - 15.1% and 18.9%, respectively. The lowest prevalence was seen in elderly patients - 4 (7.5%) subjects. Among patients who had abdominal adhesions, the age groups between 20 and 29 years old were prevalent - 18 (33.9%) subjects. Slightly less than 14 (26.4%) patients were operated between 30 and 39 years old. The operation was made least frequently in patients above the age of 60 - 5 (9.4%) subjects. Patients aged 40 to 49 and 50 to 59 years were intermediate - 8 (15.1%) patients for each age group. No statistically significant difference between the age intervals compared was found concerning the development of adhesions following the appendectomy ( $P < 0.001$ ).

Gender characteristics of patients without abdominal adhesions after the appendectomy were as follows: males - 17 (32.1%), females - 36 (67.9%). Females rather than males demonstrated phlegmonous form of inflammation of the vermiform appendix more frequently - 66.7% and 58.8%, respectively. As a percentage, catarrhal and gangrenous AA were more frequently seen in males/females - 23.5/19.4 and 17.6/13.94, respectively. As for the gender status, patients with intra-abdominal adhesions were distributed as follows: females - 35 (66.0%), males - 18 (34.0%). Catarrhal inflammation of the appendix in females/males (%) was 22.8/27.7; phlegmonous - 65.7/50.0; gangrenous - 11.4/22.2. Variations by gender status for abdominal adhesions and the incidence of different forms of AA in the comparable groups were statistically unreliable ( $P < 0.05$ ).

Of 53 patients without abdominal adhesions, 29 (54.7%) patients had 34 comorbidities including CHD, angina - 10 (18.8%) cases, hypertension - 8 (15.1%) cases, chronic cholecystitis - 6 (11.3%) cases, diabetes mellitus - 5 (9.4%) cases, gastric ulcer, gastritis - 3 (5.7%) cases, gynecological disorders - 2 (3.8%) cases. Fifty-three subjects with intra-abdominal adhesions who had undergone appendectomy had 72 comorbidities. Propensity for excessive scarring - 17 (32.1%), gastrointestinal disorders - 13 (24.5%), allergy and connective tissue systemic diseases - 11 (20.8%) for each were the most frequent. Female reproductive system disorders, CHD, hypertension, diabetes mellitus, lung disorders were much less common (3 to 5 cases). Comparing the nature of these comorbidities in the two groups of patients, it is noteworthy that patients with abdominal adhesions showed them 2.1 times more often. In addition, disorders like propensity to excessive scarring, gastrointestinal problems and allergy remarkably prevailed.

Among those comorbidities, clinical and phenotypical characteristics of patients were individually analyzed to use this criterion to predict the development of adhesive process in the abdominal cavity. During the inspection, the outer phenotype expressions of CTDS yielding cumulatively 13 scores in patients without adhesions were identified in 27 (50.9%) subjects while it was only in 14 (26.4%) subjects with intra-abdominal adhesions.

Surgical records on patients with abdominal adhesions following the appendectomy were examined and the following data were obtained: vermiform appendix was situated in the right iliac fossa in 32 (60.4%), behind the cecum in 7 (13.2%), in the pelvis in 6 (11.3%), in the retroperitoneal space in 5 (9.4%) and under the liver in 4 (7.5%) patients. Thus, atypical localization of appendix was noted in 21 (39.6%) examined individuals. In case of no abdominal adhesions after the appendectomy, typical localization of the appendix was seen in 41 (77.4%) operated subjects. In other cases, it was identified in the following locations: pelvis and behind the cecum in 4 (7.5%) subjects each; in the retroperitoneal and subhepatic space in 2 (3.7%) subjects. Atypical localization of the vermiform appendix was seen in 12 (22.6%) subjects.

Acetyltransferase activity in patients is commonly used as a criterion allowing the assessment of the propensity for post-operational adhesions. The overwhelming majority of the examined patients had a fast acetylator phenotype - 49 (92.5%) subjects; the development of adhesions found in 5 (7.5%) operated subjects

with slow acetylator phenotype was associated with post-operation complications. The mean percentage of acetylation in patients

with adhesions was  $6.31 \pm 0.23\%$  while it was  $42.7 \pm 1.25\%$  in patients without adhesions which is characteristic of subjects of slow acetylator status.

Prognostic factor	Patients, %		t	p
	with adhesions	w/o adhesions		
Quetelet index:				
18.5 - 24.9	39.7 ± 3.22	62.3 ± 5.14	3.7	> 0.05
25.0 - 29	45.2 ± 4.2	30.2 ± 3.7	2.68	
30.0 - 34	15.1 ± 3.1	7.5 ± 1.9	2.09	
Comorbidity:				
Propensity for excessive scarring	16.04 ± 203	1.9 ± 0.74	2.72	> 0.05
Gastrointestinal problems	28.3 ± 3.02	5.9 ± 1.65	3.05	
Allergy	10.4 ± 1.13	1.9 ± 0.84	2.37	
CTDS	26.4 ± 2.45	50.9 ± 3.94	3.37	
Appendix location				
Right iliac region	60.4 ± 4.23	77.4 ± 4.26	3.31	> 0.05
Atypical	39.6 ± 2.64	22.6 ± 1.9	2.14	
Acetylation type:				
Fast	92.5	52.8	2.54	> 0.05

**Table 1:** Statistical significance of prognostic factors in patients with/without adhesions.

Results of calculating confidence interval for the diagnostic tests and statistical significance between groups are presented in table 1.

Summarizing the analytical results concerning patients operated due to AA, the following factors suggest the propensity of patients to postoperative abdominal adhesions: obesity which is a controlled risk factor; acetylation status, propensity for excessive scarring, appendix location, allergy, gastrointestinal disorders, absent CTDS which are uncontrolled risk factors. Considering the informative value of these criteria, they shall be considered risk factors contributing to the development of postoperative intra-abdominal adhesions in patients with AA.

Criteria developed based on 360 operated AA patients were used to form a group of patients requiring preventive anti-adhesion treatment. In aggregate, patients had normal BMI - 205 (56.9%). Individually, the smallest number of these patients were in control group 1- 68 (56.7%); they were 6.7% more in control group 2 and 4.2% more in the main groups. Degree IIa-IIb obesity was noted in 47 (13.1%) operated patients, however, the distribution between groups was equal ( $P > 0.05$ ) with almost every fifth overweight patient having AA.

The vermiform appendix was situated in the right iliac fossa in most patients - 284 (78.9%). Much less common location was behind the cecum (33 - 9.2%), in the pelvis (21 - 5.8%); even less frequent - under the liver (12 - 3.3%) and in the retroperitoneal space (10 - 2.8%).

The following comorbidities in patients of the main group, as well as of both groups were the most common: propensity for excessive scarring with the average of 23.3%; drug and food allergy - 20.8% and gastrointestinal problems - 14.2%. Other disorders including gynecological, digestive disorders, atherosclerosis and CHD were much less frequent and could not suggest a propensity to scar formation.

CTDS was diagnosed by an aggregate score of the external phenotypic expressions and then confirmed by histology in 42 (35.0%) patients with AA of Group 1; 45 (37.5%) patients with AA who underwent laparoscopy and 48 (40.0%) patients of the main group.

Fast acetylator phenotype was found in 149 (41.4%) patients with AA. Of 211 (58.6%) patients with AA having slow acetylator phenotype slightly superior to the fast type, 24 (8.0%) patients with atypical appendix localization, present comorbidities includ-

ing overweight, gastrointestinal disorders, allergy and overscar- ring frequently combined with intraperitoneal adhesions without CTDS have been additionally assigned to the group of high risk of postoperative abdominal adhesions.

In summary, prevention of postoperative intra-abdominal adhe- sions was required in 173 (48.1%) patients with AA.

Enzyme-linked immunosorbent assay (IEA) was used to test blood serum in different dilutions in 360 patients who underwent appendectomy on Day 3 to 4 after the surgery with magnoimmu- nosorbent diagnostic test-systems (MIS) with adhesion antigen complex (AAC) as protein ligand separated from intra-abdominal adhesions of the operated patients. A titer of 1:80 was a diagnostic serum dilution ratio. Based on IEA findings, a propensity for ab- dominal adhesions was detected in 188 (52.2%) patients with AA. As the dilution was increased, the number of reactions declined markedly reaching a minimum of 3.9% at a dilution of 1:640. For a diagnostic titer of 1:80, a positive agglutination reaction was at- tained in all 149 patients who had fast acetylation type. Among patients with slow acetylation activity whose serums reacted with MIS were 24 (6.7%) patients previously assigned into the group of high risk of developing severe abdominal adhesions. The use of MIS was furthermore instrumental in detecting a propensity to abdom- inal adhesions in 15 (4.1%) subjects. Of them, 3 (0.8%) patients were of control group 1; 8 (2.2%) of control group 2 and 4 (1.1%) were of the main group.

For various reasons (patient's refusal from anti-adhesion treat- ment or present counterindications for that treatment, nonresi- dent patients, etc.), 29 (8.1%) patients received no anti-adhesion therapies (control group). Among them, there were 10 patients of control group 1, 11 patients of control group 2 and 8 patients of the main group. By Day 15 post-operation, 24 (82.7%) patients dem- onstrated positive results of IEA diagnostic serum dilution suggest- ing potential postoperative adhesions. During the follow-up period, this value reduced to 18 (62.1%) by Day 30 and to 10 (34.5%) by Day 45. In non-diagnostic dilutions (1:160 - 1:640), similar ten- dency was registered in which there were just as 10 positive anti- gen-antibody reactions at a maximum dilution of 1:640 suggesting intra-abdominal adhesions in these patients. Among them, there were 6 patients of control group 1, 3 patients who underwent lapa- roscopic appendectomy, and 1 patient in whom a multi-modality treatment approach was used. The presence of intra-abdominal

adhesions was confirmed in 8 patients by US examination done during an outpatient examination within 1.5 to 2 months after the surgery, and in 2 patients by CT during an examination due to hep- atic disorders.

The remaining 159 (44.2%) patients with AA prone to the de- velopment of postoperative adhesions received stagewise anti- adhesion therapies: 0.9% solution of 100 ml at a concentration of 1.3 mg/l i.v. 2 times daily 1 to 3 days after surgery; fragmin 0.3 ml/ daily (clexane 0.4 ml/daily) secondary to coexisting moderate hy- percoagulation starting from day 2 to 3 post surgery; 3000 U lon- gidaza (bovhyaluronidaze) 1 time every three days starting from day 5 after the appendectomy to reduce viscosity of hyaluronic acid and collagen availability for fibroblasts to prevent adhesion forma- tion; magnet therapy from day 4-5 post surgery with the pulsed magnet field induction force of 4- 5 mT, pulse rate of 10 Hz for 10 minutes; infrared radiation 4.5 mW with the rate of 1500 Hz and exposure time of 2 minutes; at week 3-4 post surgery, outpatient, phoresis of Longidase 500 U with the buffer solution no. 5-7 classic method by "Potok-1", system with the exposure duration of 15 min- utes. The dynamics of IEA agglutination reactions in 159 patients who received a multimodality anti-adhesion therapy is shown in figure 1.

**Figure 1:** IEA quantitative characteristics in patients who received anti-adhesion therapy.

Positive IEA results in blood serums of 159 patients with AA at a diagnostic dilution of 1:80 with MIS tended to decline by Day 45 from 114 (71.7%) to 14 (8.8%). The number of patients whose blood serums were IEA-MIS positive at non-diagnostic dilutions (1:160 - 1:640) secondary to the treatment gradually declined to 14 (8.8%). Among those were 7 subjects of control group 1, 4

subjects after the laparoscopic appendectomy and 3 subjects who received multimodality therapy. Thus, the number of antigen + an-

tibody reactions during the anti-adhesion treatment declined suggesting a positive effect (Table 2).

Symptom	Score 1-10	Anti-adhesion treatment					
		Was not performed			Performed		
		abs.	%	risk	abs.	%	risk
Imaging results	3	10	34.5	103.5	14	8.8	26.4
Autoantibody production	7	15	51.7	361.9	22	13.8	96.6
Total		465.4			123.0		

**Table 2:** Risk to develop intra-abdominal adhesions as evidenced by treatment results (Day 45).

The risk of developing intra-abdominal adhesions during anti-adhesion treatment in prone patients declined by 3.8.

In a total of 188 patients with AA prone to postoperative intra-abdominal adhesions, 10 (34.5%) of 29 operated who rejected anti-adhesion treatment and 14 (8.8%) of 159 patients who received anti-adhesion therapy had adhesions. Altogether, abdominal adhesions were identified in 24 (12.7%) subjects: in 13 (6.9%) after open appendectomy, in 7 (3.7%) after laparoscopy, and in 4 (2.1%) treated using multimodality approach.

**Conclusion**

- Propensity to the development of postoperative intra-abdominal adhesions is suggested by: controlled risk factors including obesity; uncontrolled risk factors including acetylation status, propensity for excessive scarring, appendix location, allergy, gastrointestinal disorders, absent CTDS.
- In patients with acute appendicitis, a propensity for postoperative adhesions shall be identified and a high-risk group requiring prevention therapy shall be formed.
- Anti-adhesion treatment in high-risk patients allowed to reduce the probability of developing abdominal adhesions by 3.9 times - from 34.5% to 8.8%.
- A multifaceted approach to treat patients with acute appendicitis allowed to reduce the development of postoperative abdominal adhesions by 3.23 times compared to open appendectomy and 1.75 times compared to laparoscopy.

**Compliance with Ethical Standards**

- The authors of the present study do not have any relevant conflict of interests to declare.

- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
- All institutional and national guiding principles regarding the laboratory animal care and use were observed.
- The informed consent for research was received from all patients.

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