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RESEARCH ARTICLE

The Effect of Symptom/Waiting Periods and Appendectomy Timing on Clinical Outcomes in Patients with Appendectomy

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ABSTRACT

Aim: To examine the effects of pre-hospital and pre-operative hospital time and timing of surgery on clinical outcomes in patients with acute appendicitis (AA).

Method: Patients who underwent appendectomy between January 2015 and June 2020 were included. Demographic data, operation/anesthesia type, American Society of Anesthesiologists score, hospital admission times, hospital preparation time and total time (sum of duration of symptoms plus hospital preparation time), operation timing, peroperative findings and complications were evaluated.

Results: In total 1,865 cases were reviewed. The mean duration of symptoms was 20.7 hours, the mean preparation time was 14.5 hours, and the mean total time was 35.2 hours. In terms of operation timing and complication rates these were: 25.6% between 08:00-16:00 (5% complication rate); 41.9% between 16:00-24:00 (3.1% complication rate) and 32.5% between 24:00-08:00 (5.9% complication rate). When evaluated in terms of duration of symptoms and complications, this period was longer in the group with complications (20.4 versus 37.4 hours). When evaluated in terms of total time, it was found that this period was significantly longer in patients who developed complications (34.8 hours vs 42.4 hours, p=0.004). Duration of symptoms ≥11.5 hours was significantly associated with the development of complications. Furthermore, the complication rate increased when the total time was ≥30.5 hours.

Conclusion: The time from the onset of symptoms to appendectomy in AA is closely associated with the development of complications. Patients admitted to the hospital ≥11.5 hours after the onset of symptoms or operated ≥30.5 hours after symptom onset have an increased complication rate after appendectomy.

Keywords: Acute appendicitis, appendectomy, surgical outcomes, timing of the operation

Introduction

The lifetime incidence of acute appendicitis (AA) is around 8% and it is one of the most common causes of acute abdomen.[1] Pathogenesis of AA may be external (lymphoid hyperplasia) or internal (impacted stool, appendicolitis) compression, both types leading to lumen obstruction. This obstruction leads to increased mucus production, bacterial overgrowth, and stasis, which increase appendiceal wall tension.[2] Consequently, the decrease in blood and lymph flow creates a situation conducive to the development of necrosis and perforation. The incidence of complicated appendicitis progression from simple appendicitis, including gangrenous or perforated appendicitis, is 28-29%.[3,4] Postoperative morbidity rates are between 2% and 23%, which may include superficial or deep surgical site infections, adhesions, fistulas, vascular injuries, and urinary tract infections.[5,6] Appendectomy, which was first performed by Dr. Claudius Amyand in 1735, is one of the most common general surgical procedures in the treatment of AA.[7]

Recent successful trials of non-operative treatment of mild/moderate appendicitis predict that short delays may be

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possible before planned emergency surgery.[8] Although delaying surgery increases the development of complicated appendicitis and post-operative complications,[9,10] controversy continues regarding the timing of appendectomy. Factors affecting the timing of the appendectomy include the patient's clinical picture, as well as the facilities available in the treating hospital, such as physical conditions or number of staff. Elective surgery lists and life-threatening emergencies are also important factors in delay.[11,12] There are a number of known potential disadvantages of emergency surgery and, sometimes, night surgery. In addition, there are reports that patient-related factors[9,13] have more effect than hospital-related factors[14,15] on the delay of treatment. Although some studies[16,17] reported higher rates of morbidity and complications associated with night surgery, no difference was found in other studies,[18,19] supporting the role of patient-related factors on AA surgery outcomes.

The aim of this study was to determine the effects of the time from the onset of symptoms to surgery and the period of the 24-hour cycle in which the appendectomy was performed on clinical outcomes and complication rates in patients with appendicitis.

Materials and Methods

The data of 1,865 patients who underwent appendectomy with a pre-diagnosis of AA between January 2015 and June 2020 in Fatih Sultan Mehmet Training and Research Hospital, Clinic of General Surgery were retrospectively analyzed. Ethics committee approval was obtained for this study from the hospital ethics committee (approval number: 30.03.2021/E-17073117-050.06). Informed consent was obtained from the patients. Parameters evaluated in the study included patient demographic data (age/gender), type of operation/anesthesia, American Society of Anesthesiologists (ASA) score, duration of symptoms, duration of preparation and total duration, defined as the sum of the former two periods, operation time divided into three periods (first period 08.00-17.00, second period 17.00-00.00, and third period 00.00-08.00), per-operative findings and data about post-operative complications in the first 30 days, based on the Clavien-Dindo classification.

The patients were examined by the emergency physician after presentation to the emergency department. Following physical examination and medical history taking, laboratory tests and ultrasound or computed tomography were planned. The time between the time when the patient first noticed symptoms such as fever, anorexia, nausea, vomiting, abdominal pain, and the time of presentation to the emergency service was defined as the "duration of symptoms". The onset time of symptoms was recorded by emergency department doctors. Later, the patient was admitted to the general surgery service with a pre-diagnosis of AA, and anesthesia preparation was completed.

Appendectomies were almost always initiated with a laparoscopic approach if there were no contraindications. Open appendectomy and/or spinal anesthesia was preferred when contraindications existed. Conversion to open surgery was at the option of individual surgeons at any stage, if the operating surgeon thought the laparoscopic procedure was unsafe.

In this study, the appendicitis was defined as simple in the surgical absence of gangrene, perforation, abscess, localized purulent fluid accumulation, and generalized peritonitis. In the presence of these findings, it was defined as complicated appendicitis.

Patients who were not diagnosed with complicated appendicitis were generally discharged within 24-48 hours, and intravenous antibiotic therapy was not used in the post-operative period, in line with the recommendations of current guidelines. In patients with complicated appendicitis, intravenous (iv) Ceftriaxone 2 g/day as two doses and iv Metronidazole 1,500 mg/day as three doses were preferred. Patients who tolerated a regular diet could be discharged when approved by the follow-up surgeon. All patients were called to the outpatient clinic after their first week of discharge. Post-operative complication was accepted as being present in patients who were admitted to the emergency department with any symptoms within the first 30 days during the follow-up period and who were subsequently hospitalized.

Histopathological evaluation of surgical excision samples was carried out by a specialist pathologist. Pathology was defined as: 1) AA, infiltration of muscularis propria with neutrophils without signs of purulent exudate; 2) Acute Suppurative Appendicitis, presence of purulent exudate in the lumen of the appendix with or without abscess formation in the appendiceal wall; 3) Acute Gangrenous Appendicitis, presence of gangrenous necrosis in the entire wall without evidence of perforation; and 4) Perforated Appendicitis, presence of roughly identifiable open perforation foci.

All patients over the age of 18 with a pre-diagnosis of AA were included in the study, while patients who underwent appendectomy for a reason other than AA diagnosis and patients with missing data were excluded from the study.

Statistical Analysis

SPSS, version 22 (IBM Inc., Armonk, NY, USA) software was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency) were used to evaluate the study data, a One-Way ANOVA test was used to compare normally distributed parameters between groups in the comparison of quantitative data. Chi-square test and

Binary logistic tests were used to compare the qualitative data. Significance was assumed when p<0.05.

Results

There was a total of 1,865 patients who underwent appendectomy for AA included in the study. The mean age of all patients was 35.2 years and 1,178 (63.2%) were male and 687 (36.8%) were female. In addition, 67.1% were ASA 1 and 99.5% of the operations were performed under general anesthesia. While 1,776 patients (95.2%) were operated using a laparoscopic method, the open method was preferred in 70 (3.8%) patients at initial surgical planning. During surgery, 19 (1.0%) were converted from laparoscopic to open surgery. Analysis of the periods of the day in which operations were performed showed that, 477 (25.6%) were operated between 08.00 and 16.00, 781 (41.9%) were operated between 16.00 and 00.00, and 607 (32.5%) were operated between 00.00 and 08.00. During surgery, 1,490 (79.9%) patients had findings consistent with AA, and 375 (20.1%) patients had findings consistent with complicated appendicitis. The mean duration of the symptoms was 20.7 hours, the mean duration of preparation was 14.5 hours, resulting in a mean total duration of 35.2 hours. While no complications were detected in 1,781 (95.5%) patients, complications were observed in 84 (4.5%) patients. The most common complication grade was Clavien-Dindo 2 (59/84; 70.2%). Histopathological examination diagnosed AA in 48.5%, phlegmonous appendicitis in 25.5%, and gangrenous appendicitis in 12.9% (Table 1).

The patients were divided into two groups based on the absence (group 1) or presence (group 2) of complication (Table 2). The two groups were similar in terms of age and gender and complication rates were similar between patients with AA and complicated appendicitis. Duration of hospital preparation were also similar between the two groups However, when complications were evaluated by the method of surgery, complications rates were 15.8% in patients with conversion, 10.0% in open operations, and 4.2% in the laparoscopic group. When evaluated in terms of the operation period, the complication rate was 5.0% in 477 patients operated between 08.00 and 16.00, 3.1% in 781 patients operated between 16.00 and 00.00, and 5.9% in 607 patients operated between 00.00-08.00. When the patients were evaluated in terms of duration of symptoms and the presence of complications, this period was 20.4 hours in group 1 and 37.4 hours in group 2, and the difference was statistically significant. When evaluated in terms of total duration, it was found that this period was longer in patients who developed complications (p=0.004). Unsurprisingly, patients with complications stayed significantly longer in hospital post-operatively (p<0.001).

Table 1. Demographic data

Gender	
Male	1178 (63.2%)
Female	687 (36.8%)
Age	35.16±13.9 (15-84)
ASA	
I	1252 (67.1%)
II	478 (%5.6)
III	125 (6.7%)
IV	10 (0.5%)
Method of operation	
Open	70 (3.8%)
Laparoscopic	1776 (95.2%)
Conversion	19 (1%)
Application time	20.69±20.06 (1-168 h)
Waiting time in the hospital	14.53±10.92 (1-192 h)
Total duration	35.18±23.80 (6-240 h)
Operation period	
Period 1 (08-16)	477 (25.6%)
Period 2 (16-24)	781 (41.9%)
Period 3 (24-08)	607 (32.5%)
Operative finding	
Acute appendicitis	1490 (79.9%)
Complicated appendicitis	375 (20.1%)
Histopathology finding	
Acute appendicitis	904 (48.5%)
Phlegmonous appendicitis	476 (25.5%)
Gangrenous appendicitis	241 (12.9%)
Malignancy	12 (0.6%)
Perforated appendicitis	146 (7.8%)
Lymphoid hyperplasia/periappendicitis	86 (4.61%)
Complication	
No complication	1781 (95.5%)
Clavien-Dindo 1	3 (0.2%)
Clavien-Dindo 2	59 (3.2%)
Clavien-Dindo 3a	9 (0.5%)
Clavien-Dindo 3b	9 (0.5%)
Clavien-Dindo 4	4 (0.2%)
Length of hospital stay	2.12±1.79 (1-26 days)

ASA: American Society of Anesthesiologists

Table 2. Factors affecting the presence of complications

	Complication (n=84)	No complication (n=1781)	Univariate analysis	Multivariate analysis
Age	33.93	35.22	0.407[a]	-
Gender				
Female	29 (34.5%)	658 (36.9%)	0.372[b]	-
Male	55 (65.5%)	1123 (63.1%)	-	-
Type of operation				
Open	7 (8.3%)	63 (3.5%)	0.004[b]	0.367[c]
Laparoscopic	74 (88.1%)	1702 (95.6%)	-	-
Conversion	3 (3.6%)	16 (0.9%)	-	-
Operation period				
1	24 (28.6%)	453 (25.4%)	0.032[b]	0.590[c]
2	24 (28.6%)	757 (42.5%)	-	-
3	36 (42.9%)	571 (32.1%)	-	-
Operative finding				
A. appendicitis	64 (76.2%)	1,425 (80.0%)	0.234[b]	-
Complicated appendicitis	20 (23.8%)	356 (20.0%)		
Duration of symptoms	27.39	20.37	0.002[a]	0.311[c]
Duration of preparation	15.08	14.51	0.636[a]	-
Total duration of waiting	42.43	34.83	0.004[a]	0.805[c]
Length of hospital stay	3.05	2.08	<0.001[a]	0.002[c]

[a]One-Way ANOVA, [b]chi-square test, [c]Binary logistic

When Receiver Operator Curve (ROC) analysis was used to investigate duration of symptoms, a cut-off of ≥11.5 hours was identified for the risk of developing complications [area under the curve (AUC): 0.521 95% confidence interval (CI): 0.456-0.586; 47.6% sensitivity, 49.4% specificity, p=0.03]. When a similar ROC analysis was performed in terms of total duration of symptoms and preparation the cut-off was found to be 30.5 hours (AUC: 0.586, 95% CI: 0.523-0.650; 58.3% sensitivity, 56.1% specificity; p=0.007).

A subgroup analysis was performed in the complicated appendicitis group (Table 3). This found that the delay was higher in females compared to males in terms of both duration of symptoms and duration of preparation.

In a subgroup analysis performed in the complicated appendicitis group, the relationship between complications and age was examined (Table 4). For the duration of symptoms (11.5 hours), patients with complicated appendicitis were significantly older than patients with simple appendicitis (p<0.001). Similarly, for the total duration of waiting (30.5 hours), the complicated appendicitis group was again found to be significantly older than the simple appendicitis group (p=0.003).

Table 3. The effect of gender on the development of complications during the time until surgery

	Female	Male	p
Duration of symptoms	22.52±21.55	19.61±19.06	0.003[a]
Duration of preparation	15.87±13.44	13.75±90.5	<0.001[a]

[a]One-Way ANOVA

Table 4. The effect of age on the development of complications during the period until surgery

	Age	p
Duration of symptoms		
≥11.5 h	36.16±14.63	<0.001[a]
<11.5 h	33.61±12.55	
Total duration of waiting		
≥30.5	36.23±14.59	0.003[a]
<30.5	34.30±13.27	
[a]One-Way ANOVA		

Discussion

In this study, it was observed that the prolongation of the time from the onset of symptoms to surgery in patients who underwent appendectomy with a diagnosis of AA increased complications in the post-operative period and prolonged the length of hospital stay. This delay was related to duration of symptoms rather than duration of preparation.

Currently, although the suggestions on the timing of appendectomy are contradictory, only two guidelines[20,21] make recommendations about timing. The meta-analysis used by these guidelines reported that there was no significant difference in complicated appendicitis rates if the delay was less than 12 hours or up to 24 hours. The 2016 World Society of Emergency Surgery guidelines[20] concluded that a 12-24 hour delay in hospital for simple appendicitis did not have adverse effects on clinical outcomes. In contrast, The European Society of Endoscopic Surgery[21], which published its guide in 2016, recommended that delaying appendectomy will increase the risk of perforated appendicitis and complications, therefore appendectomy should be performed as quickly as possible.

A study by Ditillo et al.[2] showed that the severity of the pathological diagnosis and the risk of developing complications are proportional to time, and that delaying appendectomy is associated with a poor prognosis. They found that the delay in the time of the patient's transportation to the hospital was more closely related to the worsening of the pathology than delays occurring in the hospital. Similar findings were previously reported in two different series but with a much smaller number of patients (114 and 95, respectively). Since it does not seem possible to ameliorate the delay in admission to the hospital, every effort should be made in hospital in order to diagnose these patients rapidly and speed up their operations.[2]

Many studies have been conducted evaluating the effect of the time interval from hospital to surgery on results in patients with AA.[22,23] In addition to studies reporting that waiting for 12 hours or more significantly increased the risk of perforation and complications,[22] another analysis including 4529 patients showed that surgical site infections increased if the delay was ≥6 hours.[24] In contrast, in another study by Shin et al.[25], it was reported that an eight-hour threshold did not create a significant difference in results between subgroups waiting for the operation. Some other studies have found that waiting for 24 hours does not pose any risk.[26,27]

Numerous studies have shown a direct relationship between the time to surgery and complications.[22,28] Although surgeons try to avoid a possible delay for their operations, it is not always possible for the patient to be operated quickly. The diagnostic process or scheduled consultations with patients with comorbidities may take time. Limitations in operating room availablility may also delay the surgery. In addition, since the admission of patients with AA is often in the evening or after midnight, as in our study, the limited number of healthcare staff at these hours constitute other reasons for the delay. While 18 hours was the threshold in the study of Lee et al., 11.5 hours was found to be critical for the development of complications in our series.

The most important issue regarding the delay of appendectomy is the risk of perforation, as this leads to increased morbidity and mortality rates and longer hospital stays. Busch et al.[22] found that the risk of perforation increased with time and a threshold of 12 hours was critical in this process. Temple et al.[9] concluded that most perforation occurred due to a delay in admission.

In analyzes conducted to investigate the effect of gender on the occurrence of complications, the differences identified may be due to differences in perception of pain between genders. Studies have noted that females have more clinical pain.[29] Another analysis showed that longer duration of preparation affected older patients and females (19%) more than males (9%). It has been found that gynecological pathologies cause symptoms indistinguishable from appendicitis, especially in females in the premenopausal period.[30] In our study, both duration of symptoms and duration of preparation were found to be longer in females, probably due in part to some of the causes identified in earlier studies.

Anatomical and physiological changes in the appendix have been suggested as a reason for the rapid progression of the disease at older ages.[31] Although it has been reported that age did not make any difference in terms of the degree of inflammation, it was found that a significant portion (37%) of patients with complicated appendicitis were over the age of 50 years.[14,32,33] In our study, simple and complicated appendicitis groups were found to be similar in terms of age. However, the age difference between the complicated appendicitis group and the simple appendicitis group was statistically significant and in favor of the complicated group in the subgroup analysis.

Study Limitations

The limitation of this study is the retrospective analysis of data from a single hospital, and the small number of patients who developed complications despite the large overall cohort size.

Conclusion

A significant relationship was found between delayed surgery and postoperative complication rates in patients

with AA. The most important factor affecting the delay time is the prolongation from the onset of the patient's symptoms to admission to the hospital. Both duration of symptoms and duration of preparation were found to be longer in female patients. Total duration exceeding 30.5 hours increases the rate of complications after appendectomy.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study from the hospital ethics committee (approval number: 30.03.2021/E-17073117-050.06).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M.F., N.E.B., A.E., Concept: M.T.A., A.T.F., Z.Y., Design: H.Ç., N.E.B., Data Collection or Processing: H.Ç., A.E., Analysis or Interpretation: A.T.F., Y.G., Y.Ö., Literature Search: M.T.A., İ.T., Z.Y., A.C.B., Writing: M.M.F., M.T.A.

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