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ORIGINAL ARTICLE

Monitoring C-reactive protein levels during medical management of acute appendicitis to predict the need for surgery

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Abstract
Purpose To clarify the role of medical treatment in the management of acute appendicitis and the value of C-reactive protein (CRP) for predicting its failure.
Materials and methods Patients with clinically diagnosed acute appendicitis, confirmed by imaging studies, were enrolled in this study. We measured leukocyte counts and CRP levels and recorded success and recurrence rates and the efficiency of medical treatment during follow-up. The efficiency of CRP values to predict failure of medical treatment was evaluated using receiver operating characteristics (ROC) curve analysis.
Results The subjects comprised 193 patients (mean age 30.9 years) who received medical treatment for acute appendicitis. The mean follow-up period was 12.3 (6–24) months and the early success rate of medical treatment was 86.5 % (160/185). Fifteen (9.3 %) patients suffered recurrence during follow-up. The leukocyte and CRP levels in these two groups of patients were not significantly different at the beginning of the treatment, but the increase in the CRP value differed significantly between the two groups during the follow-up period ($p < 0.001$). ROC curve analysis suggested that the optimum CRP cut-off point for unsuccessful medical treatment was 80.8 mg/L, with 81.82 % sensitivity and 84.34 % specificity ($p < 0.001$).
Conclusion The success rate for treating acute appendicitis medically is high, with antibiotic treatment being effective as the firstline therapy for many unselected patients. An increase in CRP levels to 80.8 mg/L and above seems to be a meaningful parameter for determining a lack of response to medical treatment.

Keywords Appendicitis · CRP · Non-operative antibiotic treatment · Prospective study

Introduction

Acute appendicitis is the most common cause of acute abdomen requiring surgery. It is often considered a disease of adolescents and young adults, with its frequency peaking in the second and third decades. For a long time after McBurney first described appendectomy in 1889 [1], the undisputed treatment for acute appendicitis was surgery. Yet, in the absence of peritonitis many intraabdominal inflammatory processes such as diverticulitis have been treated medically. Many recent studies show that uncomplicated acute appendicitis can also be treated medically with low morbidity and cost [2, 3]. This study aims to clarify the role of medical treatment in acute appendicitis and establish the value of measuring the C-reactive protein (CRP) level to predict resistance to medical treatment.

Materials and methods

The study was carried out prospectively with the permission of the ethical committee of Selçuk University Meram

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Modified alvarado score	
Symptoms	**Score**
Migratory right iliac fossa pain	1
Anorexia	1
Vomiting / Nausea	1
Signs	
Tenderness right lower quadrant	2
Rebound tenderness right lower quadrant	1
Pyrexia ≥ 37.5°C	1
Investigation	
Leucoctosis	2

Fig. 1 Modified Alvarado score

Faculty of Medicine. Informed consent for medical treatment was obtained from all of the patients enrolled.

All patients older than 18 years, who were admitted to our clinic with a pre-diagnosis of acute appendicitis, were evaluated for this study. We used a modified Alvarado Score (MAS) for clinical evaluation (Fig. 1). Patients with an MAS of 6 and above underwent ultrasonography (USG) as the primary imaging study. When the appendix could not be seen on USG, abdominal computed tomography (CT) with intravenous contrast was used. The main criteria for diagnosing acute appendicitis on CT and USG were periappendiceal inflammatory changes, an appendix with a diameter of more than 6 mm, or wall thickness greater than 3 mm. The Alvarado score was taken as a basis for the diagnosis. Each patient with a confirmed diagnosis of acute appendicitis based on imaging studies signed the informed consent form. All those patients were given the option of medical treatment and those who accepted this treatment option were enrolled in the study.

Medical treatment consisted of the cessation of all oral intake, with fluid-electrolyte replacement and antibiotic therapy, as ciprofloxacin 200 mg/100 ml twice a day, metronidazole 500 mg three times a day IV, and diclofenac sodium 50–75 mg twice a day IM. Patients were monitored closely by clinical examination and daily measurement of the leukocyte count and CRP levels. When the pain did not resolve and examination findings worsened, appendectomy was performed after discussion with the patient. When the pain resolved and examination findings stayed stable, patients were allowed oral fluids initially and graded up to free food intake. The patients were discharged within 48–72 h after follow-up abdominal USG or CT.

The patients went home on oral antibiotherapy with ciprofloxacin 500 mg (twice a day) and metronidazole 500 mg (three times a day) for 7 days. They were called in for follow-up 7 days and then 1 month after discharge. At their follow-up visits, they were asked about their pain and then underwent physical examination and had their leukocyte count and CRP levels measured. They also underwent repeat imaging, using the same modality as at the time of diagnosis. Thereafter, the patients were followed up by phone, 6 and 12 months after discharge. The patients who presented again with clinical, laboratory and imaging signs of acute appendicitis after discharge were considered to have suffered recurrence and were treated either medically, if they accepted this option, or surgically if necessary.

Patients were divided into two groups according to whether medical treatment was successful (group 1) or unsuccessful (group 2) and the leukocyte and CRP values were compared. Patients who did not accept medical treatment, those who were younger than 18, and those were pregnant were excluded from the study. Patients whose Alvarado Score was lower than 6 and were clinically suspected of having acute appendicitis and those whose Alvarado score was higher than 6 and a diagnosis of acute appendicitis was not supported radiologically (USG-CT) were also excluded, as were patients with complications such as peritonitis, a periappendicular mass, or abscess formation seen on imaging studies.

Data were evaluated using SPSS 16.0 (SPSS Inc., 2009, Chicago, IL, USA) for Windows program. $p < 0{,}05$ was considered significant. The paired t test was used for intragroup comparison and an independent sample t test was used for intergroup comparison. The CRP levels in relation to the prediction of failed medical treatment were evaluated using receiver operating characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity and specificity were calculated.

Results

Of total 235 patients admitted to our clinic with acute appendicitis between December 2010 and September 2012, 193 who accepted medical treatment and met the study criteria were included in the analysis (101 men, 92 women; mean age, 30.9 years). There was no significant difference between the groups in terms of age and gender (Table 1). The mean follow-up period was 12.3 (6–24) months.

Table 1 Demographic data of the patients

	Group 1 ($n = 160$)	Group 2 ($n = 25$)	p value
Mean age (years)	31.12 ± 13.1	29.48 ± 5.9	0.5
Sex (%)			0.65
Female	91 (56.9)	9 (36)	
Male	69 (43.1)	16 (64)	

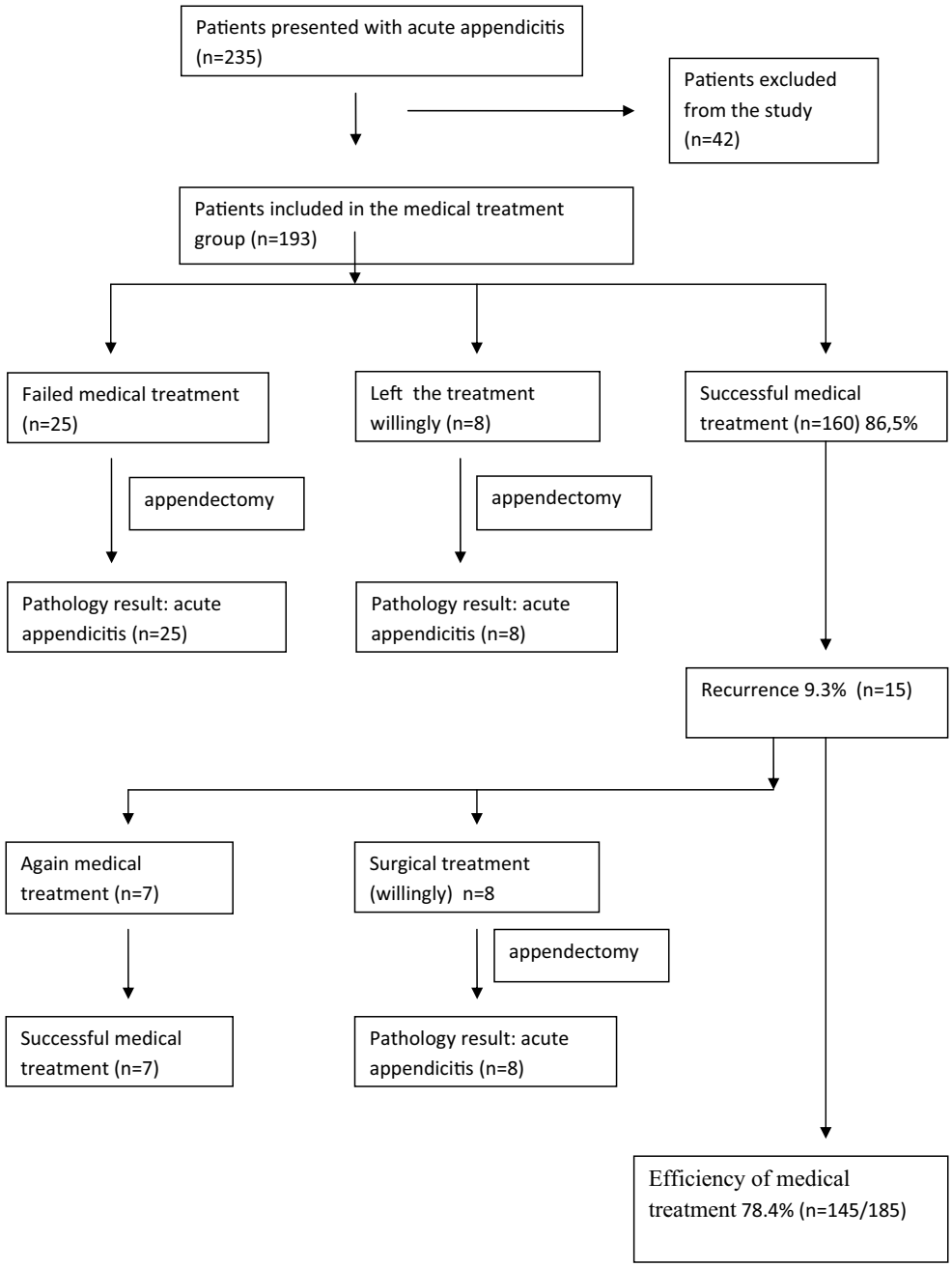

Fig. 2 Flow chart of the results of this study

As the clinical findings either did not regress or they worsened in 25 patients, the responsible clinician decided that medical treatment had failed and those patients underwent surgery. A further eight patients decided to abandon medical treatment and undergo elective surgery. The diagnosis of acute appendicitis was confirmed by both intraoperative findings and pathology in all patients who underwent appendectomy. No pathology was found other than appendicitis. Thus, the medical treatment success rate was 86.5 % (160/185). Recurrence developed in 15 patients: in the first 6 months in 10, within 6–12 months in 4, and after 13 months in 1. We recommended the same medical treatment to all these patients, but eight did not accept this option and underwent appendectomy. The other seven was successfully managed with medical treatment again.

Screening was done for all patients with an Alvarado score of 6 or above, to confirm the diagnosis. USG was done routinely for all patients and if this showed no

Table 2 Comparison of the white cell count and C-reactive protein levels in the two groups

Groups	First Wbc (K/mm3)**	Last Wbc (K/mm3)***	First CRP (mg/L)	Last CRP (mg/L)	Length of hospital stay (days)
Group 1 (successful)	12.35 ± 5	8.75 ± 2.8	43.13 ± 49.6	34.12 ± 42.6	2.32
Group 2 (unsuccessful)	13.25 ± 2.2	9.35 ± 1.5	37.28 ± 29.4	113.6 ± 53.2*	2.14

* $p < 0.05$

** WBC and CRP levels at the time of presentation

*** WBC and CRP levels at the time of discharge

evidence of appendicitis, CT scan was done. Patients who had no sign of appendicitis on USG and CT images were excluded from the study. CT scan was done for 23 patients without evidence of appendicitis on USG. Figure 2 summarizes the data of this study.

The leukocyte values of the 25 patients in whom medical treatment failed (group 2) and the 160 patients in whom medical treatment was successful (group 1) returned to normal post-treatment. There was no significant difference between the groups in the leukocyte count or CRP levels at the beginning of the treatment (Table 2). The groups were also similar in terms of age and sex. However, the CRP levels increased up to 100 and above in 18 of the 25 patients resistant to medical treatment 9 (group 2). On the other hand, in group 1, only five patients had an increase in CRP levels to above 100. In one of these patients, a periappendicular abscess developed, which was percutaneously drained on day 7 of the treatment. The difference between the groups in CRP increase was significant in the follow-up period ($p < 0.001$). The ROC curve analysis suggested that the optimum CRP cut-off point for failed medical treatment was 80.8 mg/L with 81.82 % sensitivity and 84.34 % specificity (95 % CI 0.795–0.937; $p < 0.001$) (Fig. 3).

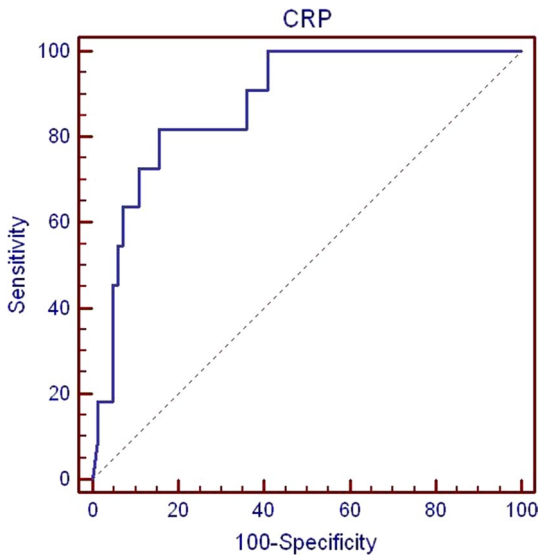

Fig. 3 Receiver operating characteristic (ROC) curves of C-reactive protein (CRP) for the patients in whom medical treatment for appendicitis failed

Discussion

Acute appendicitis is the most common emergency operation performed in the field of general surgery. From the time of the original definition of appendectomy by McBurney until very recently, acute appendicitis was always treated surgically as the standard, with general consensus among all surgeons in this regard. However, this belief is being shattered by many recent studies demonstrating that acute appendicitis can often be treated medically like other intraabdominal inflammatory processes [2–4]. Although early surgery is still often recommended for acute appendicitis, medical treatment is now considered a feasible option because of increasing morbidity in the presence of complications such as periappendicular abscess or a mass [5]. In fact, 90 % of patients with complicated acute appendicitis can be treated medically [6, 7]. While medical treatment used to be considered as simply a bridging treatment for appendectomy, evidence now suggests that appendectomy should not be done routinely [5, 7]. With routine interval appendectomy, morbidity, hospital stay, and costs all increase [8]. However, colon malignancy must be excluded in patients who are older than 40 and interval appendectomy is not recommended in pediatric patients because of the high risk of recurrence. The Alvarado score was an effective system for establishing acute appendicitis and reducing the negative appendectomy rates; however, additional diagnostic methods such as USG and CT are recommended, especially in patients with an Alvarado score between 4 and 8. Considering the high cost and negative effects of CT, such as radiation, we prefer to use it only when USG is impractical [9, 10].

The first randomized controlled study on the medical treatment of acute appendicitis was done by Eriksson et al. from Sweden, who divided 40 patients into two groups of 20. Of the 19 (95 %) patients in the medical treatment group, who were in fact medically treated, 7 experienced

Table 3 Studies on the medical treatment of appendicitis [2–4, 11, 13]

Study	Number of patients	Success of the medical treatment (%)	Recurrence rate (%)	Median length of follow-up	Efficiency of the medical treatment
Eriksson S	20	95	36	12 months	60
Styrud J	128	86	11	12 months	76
Hansson J	202	92	13	12 months	79
Vons C	120	88	28	12 months	63
Turhan AN	107	82	8.4	136 days	79
Our Study	193	86	9.3	12 months	78

recurrence within 1 year of follow-up. The authors emphasized that acute appendicitis was medically treatable, but recurrence was high [11]. A multicenter prospective randomized study was then done by Styrud et al. from the same center. The results of this and other subsequent studies on the medical treatment of acute appendicitis are summarized in Table 3.

A meta-analysis of randomized controlled studies ($n = 4$) comprising 900 patients compared medical treatment vs. surgical treatment for acute appendicitis. It concluded that medical treatment was safe and effective for initial management, with lower morbidity than appendectomy. However, the hospital stay and incidence of recurrent appendicitis were not different from those of primary appendectomy. After medical treatment, recurrence was observed in nearly 20 % of patients and treatment efficiency was calculated as 63 % [12]. In light of these literature data, medical treatment for acute appendicitis is generally over 80 % (82–95 %) effective at the beginning, but a high incidence of recurrence (10–28 %) is the main problem. The relapse rate in our study was found to be lower than that documented in the literature (9.3 %), but we stress that the initial treatment should be medical when low cost and morbidity are taken into consideration, due to the absence of additional mortality in cases of recurrence [12]. Furthermore, the applicability of other medical treatments should also be taken into consideration for recurrence.

A study by Vons et al. [13] found stercolith (appendicolith) in 18 % of patients who underwent appendectomy, and complicated appendicitis was diagnosed in 40 % of these patients; as perforated appendicitis, peritonitis, or wound site infection. Moreover, appendicolith was found in 16 % of the patients in the medical treatment group, 31 % of whom did not respond to medical treatment. A relationship was established between no response to medical treatment and stercolith and complicated appendicitis in this study. Stercolith was detected in 6 patients who underwent a CT scan and medical treatment was successful for all of these patients; however, the presence of stercolith was not found to be a reason for failed medical treatment in the present study.

In reviewing all the studies, it is noteworthy that there is no standard approach to diagnosis and treatment. Diagnosis is made by history, clinical findings, and laboratory tests, as well as routine imaging in some studies, and even then only for some patients [4, 11]. Moreover, the medical treatment differs among studies. Styrud et al. administered cefotaxime 2 g (twice a day) and tinidazole 800 mg (once a day) for 2 days, parenterally; Hansson et al. administered cefotaxime 1 g (twice a day) and metronidazole 1–5 g (once a day), over a treatment period based on healing; Vons et al. administered amoxicilin plus clavulanic acid 3 g/day for 2 days parenterally; and Turhan et al. administered amphyciline 1 g (four times a day), gentamycin 160 mg (once a day), and metronidazole 500 mg (three times a day) for 3 days parenterally. The treatment was covered for 10 days by oral antibiotherapy. In the present study, ciprofloxacin and metronidazole combination were administered because of the Gram-negative, Gram-positive, and anaerobic antibacterial effects, and as the patient could continue taking the same drugs orally after discharge from the hospital. There is no consensus about this topic in the literature; thus, we gave the combination of ciprofloxacin 200 mg (twice a day) and metronidazole 500 mg (three times a day). The results of this combination seem to be similar in various studies, although there is no common treatment algorithm.

CRP is an inflammatory marker used frequently together with the leukocyte count in the diagnosis of acute appendicitis. Many studies show a positive relationship between CRP and the severity of acute appendicitis [14–17]. In our study, we researched the value of CRP for predicting resistance to the medical treatment of acute appendicitis. CRP is a marker that shows the severity of inflammation and while leukocyte counts decreased following medical treatment, no matter whether the patient responded to it, the CRP levels tended to increase in those patients who did not respond. Thus, it was seen as an indicator of non-response to medical treatment, particularly in patients in whom it increased to 80.3 and above.

We conclude that the success rate of medical treatment for acute appendicitis is high, so it should be considered as the initial treatment as its associated morbidity is low.

Recurrence seems to be the major problem; however, the recurrence rate in this series was acceptable. As clinical follow-up is the gold standard for establishing if a patient is resistant to medical treatment, the CRP level, which tends to increase, is a valuable supportive marker.

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