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Effectiveness of nonsurgical antibiotic treatment in the experimental appendicitis model in rats

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Abstract

Background: In this study, we aimed to demonstrate efficacy and laboratory follow-up criteria of nonsurgical antibiotic treatment in uncomplicated acute appendicitis. We established an experimental appendicitis model in rats, and antibiotic treatment was evaluated by biochemical and immunohistochemical changes.

Materials and method: In the study, 28 rats were divided into 4 groups. Group 1 constituted the group of sham; group 2 was the control group that appendicitis model was created and did not receive any treatment. Group 3 was created as an appendicitis model and was given regular antibiotic treatment. In group 4, appendicitis model was created, and appendectomy was performed on the 2nd day. Blood samples were taken from the rats on the 0, 2nd, and 7th days in all groups. Rats in groups 1, 2, and 3 underwent appendectomy with laparotomy under anesthesia on the 7th day. Serum C-reactive protein (CRP), procalcitonin, and leukocyte levels were measured for biochemical analysis. In immunohistochemical evaluation, inflammation severity of the tissue samples taken from appendices was evaluated. Also, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels of tissue samples were evaluated.

Results: A statistically significant difference in CRP values was observed between groups 1 and 2 on the 7th day ($p = 0.046$), between groups 1 and 4 on 0 and 2nd days ($p = 0.004$, $p = 0.004$), between groups 2 and 3 on 0, 2nd, and 7th days ($p = 0.018$, 0.013, 0.025), between groups 2 and 4 on 0, 2nd, and 7th days ($p = 0.002$, $p = 0.002$, $p = 0.009$), and between groups 3 and 4 on 0 and 2nd days ($p = 0.013$, $p = 0.025$). There was a significant difference in procalcitonin values between groups 1 and 3 on the 7th day ($p = 0.032$) and between groups 1 and 4 on day 0 ($p = 0.019$). A significant difference was also observed in TNF-α and IL-6 inflammation between groups 2 and 3 ($p = 0.031$, $p = 0.018$) and between groups 2 and 4 ($p = 0.031$, $p = 0.01$).

Conclusion: Acute uncomplicated and early appendicitis may be treated with antibiotics. According to our results, CRP levels are useful as follow-up criterion in experimental appendicitis model. Clinical studies on the assessment of CRP levels in the course of nonsurgical treatment in the patients with acute appendicitis will reveal out the effectiveness of this marker.

Keywords: Appendicitis, Nonsurgical treatment, Antibiotic treatment, Experimental study, Rat

Background

Appendicitis is the most common emergency pathology in childhood. When appendicitis is examined without age and sex, it is seen in 7–8% of the population. It can be seen in children at any age, including the newborn period. However, appendicitis is most frequently seen in children between 11 and 12 years of age. Treatment

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of appendicitis has been an emergency appendectomy for many years. It is known to the surgeons that some patients who have been diagnosed with appsendicitis and who have started antibiotic treatment tend to have clinical improvement in the period before appendectomy. Then, the surgeons began to treat appendicitis only with antibiotics as small case series [1, 2]. Nonoperative treatment for nonperforated appendicitis in children is safe and efficient [3]. The clinical and laboratory follow-up criteria during hospitalization of the patients were heterogenous in the published studies, and no any experimental study was done up to date for showing pathological changes of the appendix during the conservative therapy regimen [4, 5].

In this study, we aimed to demonstrate efficacy and laboratory follow-up criteria of nonsurgical antibiotic treatment in uncomplicated acute appendicitis. We established an experimental appendicitis model in rats, and antibiotic treatment was evaluated by biochemical and immunohistochemical changes.

Materials and method

Animals and experimental surgery

The study was conducted in the University Experimental Animals Research and Application Center and was approved by the Faculty Ethics Committee of Animal Experiments. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Ethical rules of international animal experimentation have been followed throughout the study. Also, the study was funded by the University Scientific Research Projects Office.

In the study, 28 animals of Sprague-Dawley genus 200–250 gr were used. Animals were divided into 4 groups. Group 1 constituted the group of sham; group 2 was the control group that appendicitis model was created and did not receive any treatment. Group 3 was created as an appendicitis model and was given regular antibiotic treatment (treatment group). In group 4, appendicitis model was created, and appendectomy was performed on the 2nd day (appendectomy group). After intraperitoneal anesthesia with xylazine hydrochloride (15 mg/kg) and ketamine hydrochloride (100 mg/kg), animals were subjected to laparotomy with sterile staining and covering. The experimental appendicitis model was performed by ligating a small distal part of the caecum which is filled with cecal material. The suture was loosely bound so as not to disturb the circulation of the cecum wall (Fig. 1). The abdomen was then closed by suturing. In group 1, appendicitis was not performed, only laparotomy was performed, and the abdomen was closed. No treatment was given. In the second group only, appendicitis was created, and no treatment was given. In the third group, antibiotic (sulbactam 100 mg/kg — ampicillin 50 mg/kg) was given intraperitoneally daily after appendicitis. Appendectomy was performed in the 4th group 48 h after appendicitis. Blood samples were taken from the animals on the 0, 2nd, and 7th days in all groups. All animals in groups 1, 2, and 3 underwent appendectomy with laparotomy under anesthesia on the 7th day. The rats were monitored at 20–24 °C with 12 h light and 12 h darkness. Rats were followed up with oral water-solid food ad libitum.

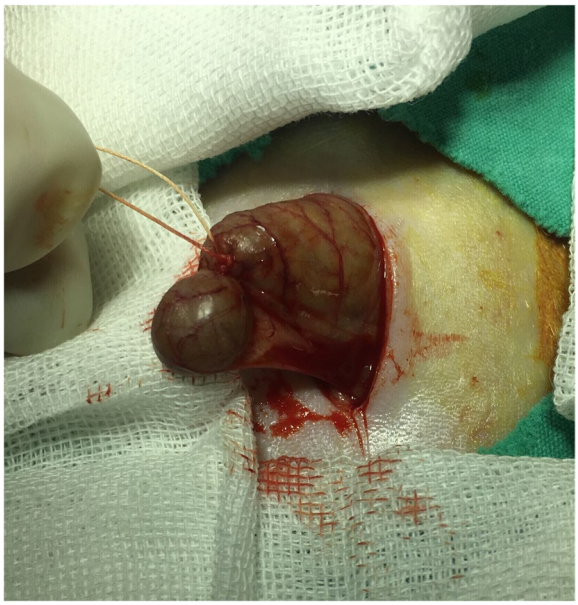

Fig. 1 The appendicitis model was obstructed with a small area vessel distal to the caecum and filled with cecal material. The suture was loosely bound so as not to disturb the circulation of the cecum wall

Biochemical analysis

Serum C-reactive protein (CRP), procalcitonin, and leukocyte levels were measured for biochemical analysis. Blood samples taken from rats for biochemical analysis were analyzed by using the original reagents from the EDTA blood sample in the analyzer (Mindray BC-6800, Biomedical Co., Shenzhen, China). Serum procalcitonin and C-reactive protein analyses were performed by enzyme-linked immunoassay (ELISA) method. The CRP analysis was analyzed with the rat-specific commercial kit (Rat CRP Assaypro LLC St. Charles, Mo, USA) according to the manufacturer's recommendations. Procalcitonin analysis was again analyzed with a rat-specific kit (Rat Elabscience Procalcitonin, Houston, Texas, USA).

Immunohistochemical staining

In immunohistochemical evaluation, inflammation severity of the tissue samples taken from appendices was evaluated. Also, TNF-α (tumor necrosis factor-alpha) and IL-6 (interleukin-6) levels of tissue samples were evaluated. The sections prepared for immunohistochemical evaluation were taken on the Isotherm Technical Laboratory Glass Materials. All preparations were placed in a fully automated immunohistochemical staining device (Ventana, Benchmark, XT IHK / ISH) for staining and immunohistochemical kit compatible with this device (ultraView Universal DAB Detection Kit and EZ prep, LCS, SSC, Cell Condition 2 (CC2), Reaction Buffer Concentrate solutions were treated using hematoxylin and Blue Reagent). For sections, 1004 g of concentrated rabbit antibody for TNF-alpha (Abcam-ab9635, rabbit polyclonal, lyophilized form) with 1:200 dilution for 1 hour 16 minutes, for IL-6 (ND50) 500 bitg concentrated mouse antibody (Abcam-ab9324, mouse monoclonal, Lyophilized 1: 250 dilutions with 1 hour incubation time.

Study and control cases were blinded to light microscopy and histopathologically evaluated. Tissue was used for TNF-α antibody and splenic tissue as positive control for IL-6. Cells with cytoplasmic expression in the mucosa were evaluated with both primary antibodies. Expression in clustered cells in the lamina propria was expressed as +1, and clusters containing 5–10 cells were evaluated as +2 (Figs. 2 and 3).

Statistical analysis

Statistical analysis was performed with SPSS software (version 20, IBM Corp.). Data are presented as mean ± standard deviations. Mann-Whitney *U*- and chi-square test was used to compare the groups. Values of p <0.05 were considered statistically significant.

Results

Results of biochemical analysis

Serum CRP, procalcitonin, and leukocyte levels were measured for biochemical analysis on the 0, 2nd, and 7th days in all groups. Results of the blood samples taken from animals in all groups are presented in Table 1 and also presented graphically in Figs. 4, 5, and 6.

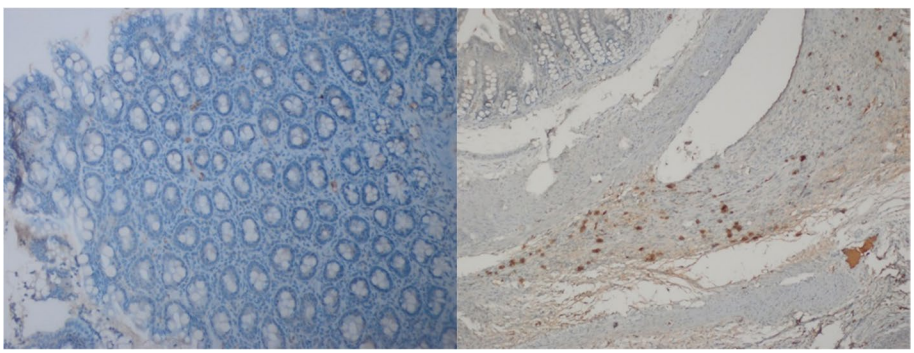

Fig. 2 TNF-α antibody, ×20. Expression in clustered cells in the lamina propria was expressed as +1 (left), and clusters containing 5–10 cells were evaluated as +2 (right)

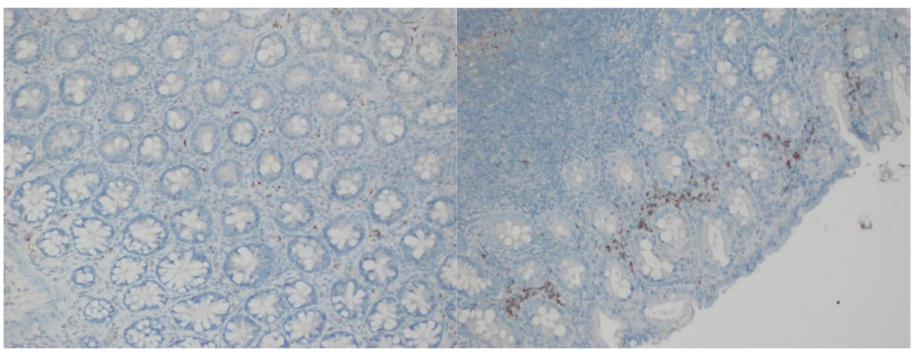

Fig. 3 IL-6 antibody, ×20. Expression in clustered cells in the lamina propria was expressed as +1 (left), and clusters containing 5–10 cells were evaluated as +2 (right)

Table 1 Biochemical results of all groups

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	Group 4 (Mean ± SD)
CRP 0 (microg/ml)	2925.2 ± 474.32	3189.28 ± 101.88	2341.42 ± 549.24	1615.0 ± 273.65
CRP 2 (microg/ml)	2993.5 ± 629.6	2998.50 ± 629.68	2348.57 ± 378.49	1914.57 ± 257.74
CRP 7 (microg/ml)	2464.66 ± 418.9	2870.142 ± 263.53	1951.57 ± 930.79	1921.14 ± 627.39
Procalcitonin 0 (pg/ml)	89.65 ± 39.44	54.39 ± 30.33	50.88 ± 30.85	29.16 ± 21.83
Procalcitonin 2 (pg/ml)	51.23 ± 43.9	27.53 ± 23.50	24.37 ± 16.73	16.28 ± 9.52
Procalcitonin 7 (pg/ml)	86.16 ± 29.4	47.62 ± 28.1	53.47 ± 40.62	43.84 ± 57.21
Leukocyte 0 (10^3/µl)	7.66 ± 2.97	9.31 ± 2.67	9.36 ± 3.60	10.20 ± 3.37
Leukocyte 2 (10^3/µl)	11.7 ± 2.66	11.50 ± 4.17	11.50 ± 4.17	10.30 ± 2.88
Leukocyte 7 (10^3/µl)	9.43 ± 2.35	9.58 ± 3.44	7.89 ± 3.69	10.53 ± 3.09

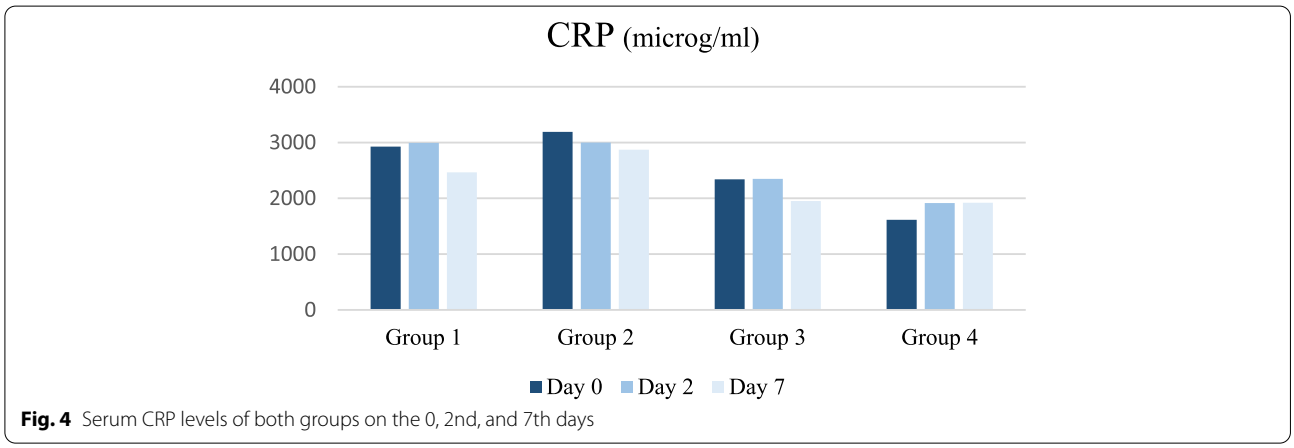

Fig. 4 Serum CRP levels of both groups on the 0, 2nd, and 7th days

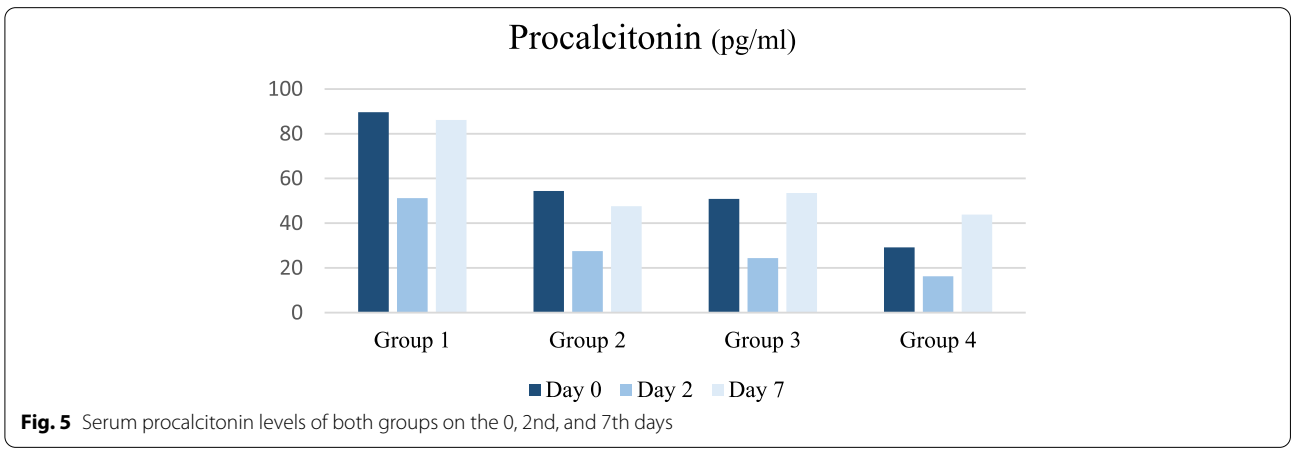

Fig. 5 Serum procalcitonin levels of both groups on the 0, 2nd, and 7th days

A statistically significant difference was observed between group 1 and group 2 in the 7th day CRP values (Mann Whitney U, $p = 0.046$). We observed that CRP increased in the late period in group 2 compared to group 1. A statistically significant difference was observed between group 1 and group 4 in terms of CRP values on days 0 and 2 (Mann-Whitney *U*, respectively; $p = 0.004$, $p = 0.004$). These results indicate that CRP is low in the surgical group in the early period. There was a significant difference between group 2 and group 3 in terms of CRP values on 0, 2nd, and 7th days (Mann Whitney U, respectively; $p = 0.018$, $p = 0.013$, $p = 0.025$). Antibiotic use leads to a decrease in the CRP levels of antibiotics between the two groups. This situation shows us

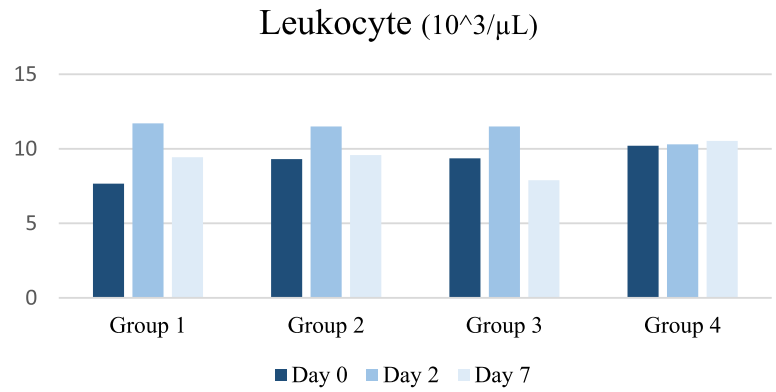

Fig. 6 Serum leukocyte levels of both groups on the 0, 2nd, and 7th days

that inflammation has regressed. As a result, antibiotic treatment decreases inflammation, and the most significant indicator is that CRP values are significantly lower in group 3 than group 2 on 2nd and 7th days. A statistically significant difference was observed for CRP values on 0, 2nd, and 7th days between group 2 and group 4 (Mann-Whitney *U*, respectively; $p = 0.002$, $p = 0.002$, $p = 0.009$). Appendectomy reduced inflammation. A statistically significant difference was observed between group 3 and group 4 in terms of CRP values on 0 and 2nd days (Mann-Whitney *U*, respectively; $p = 0.013$, $p = 0.025$).

There was a significant difference between group 1 and group 3 in the levels of procalcitonin on 7th day (Mann-Whitney *U*, $p = 0.032$). Antibiotic treatment decreases procalcitonin levels in group 3 compared to group 1 in the long term. A statistically significant difference was observed between group 1 and group 4 in terms of procalcitonin values on day 0 (Mann-Whitney *U*, respectively; $p = 0.019$). Procalcitonin values were not statistically significant between group 2 and group 3, between groups 2 and 4, and between groups 3 and 4. Leukocyte values were not statistically significant between all groups. Leukocyte counts only decreased more in group 3 on 7th day, although there was no statistical difference.

Results of immunohistochemical analysis

In immunohistochemical evaluation, inflammation severity of the tissue samples taken from appendices was evaluated. Also, TNF-α and IL-6 levels of tissue samples were evaluated. Result of immunohistochemical analysis was presented in Table 2.

There was not a significant difference between groups 2 and 3 in terms of inflammation in the mucosa, submucosa, and subserous (chi-square, respectively; $p = 0.515$, $p = 0.577$, $p = 1$). There was not significant difference between groups 2 and 4 in terms of inflammation in the mucosa, submucosa, and subserous also (chi-square, respectively; $p = 0.299$, $p = 0.84$, $p = 0.299$). Significant difference was not observed for inflammation in mucosa, submucosa, and subserous between groups 3

Table 2 Immunohistochemical results of all groups

	Inflammation	Group 1 (*n*)	Group 2 (*n*)	Group 3 (*n*)	Group 4 (*n*)
Mucosa	No	4	0	0	0
	Mild	2	1	2	0
	Severe	0	6	5	7
Submucosa	No	5	0	0	1
	Focal	1	5	4	1
	Diffuse	0	2	3	5
Subserous	No	6	0	0	1
	Yes	0	7	7	6
TNF	+1	5	1	5	5
	+2	1	6	2	2
IL-6	+1	3	0	4	6
	+2	3	7	3	1

and 4 (chi-square, respectively; $p = 0.127$, $p = 0.192$, $p = 0.299$).

A significant difference was observed in TNF-α and IL-6 inflammation between groups 2 and 3 (chi-square, respectively; $p = 0.031$, $p = 0.018$). Inflammation decreased in the group receiving antibiotic therapy. TNF-α and IL-6 were significantly different between groups 2 and 4 (chi-square, respectively; $p = 0.031$, $p = 0.01$). Appendectomy reduced inflammation. There was no significant difference in TNF-α and IL-6 inflammation between groups 3 and 4 (chi-square, respectively; $p = 1$, $p = 0.237$).

In the study model, 3 rats in group 2 were excessed in the late period (5, 6, and 7 days) without ending the study. The cause of death in autopsy findings was evaluated as widespread peritonitis. We think that the death reasons in these rats are hypovolemia, cardiac side effects, or anesthesia dependent.

Discussion

The thought of emergency appendectomy in treatment has begun to change in recent years. The pathological, radiological, and epidemiological studies revealed that appendicitis was no longer an absolute progressive disease. Yardeni, in his retrospective study, determined delaying surgery with starting antibiotic treatment until the daytime hours did not significantly affect operating time, perforation rate, or complications in children with acute appendicitis [6].

Appendicitis treatment with antibiotics in the last 20 years was first tried in adult patients. In randomized controlled trials, researchers demonstrated that acute appendicitis was effective at 41–85% in 1-year follow-up with antibiotics [7–11]. In a systematic review involving nonsurgical treatment of uncomplicated appendicitis in children, authors reported success rates of 58–100% and recurrence rates of 0.1–31.8% [12]. In another study by Tanaka, they achieved a success rate of 98.7% with nonoperative treatment [2]. In a comparative study between patients who received antibiotic treatment and patients undergoing appendectomy, they did not find an increase in the length of hospital stay and the incidence of complicated appendicitis [13]. Perforation rate was determined very low in pediatric patients treated with antibiotics for noncomplicated appendicitis [14]. In another study, it was suggested that 159 patients who were initially treated with antibiotics had only 13.8% recurrence within 2 years, and this method was useful in the treatment of appendicitis [15]. There is not any experimental study was done up to date for showing pathological changes of the appendix during the conservative therapy regimen. So, we aimed to demonstrate antibiotic efficacy in uncomplicated appendicitis in our experimental study. We established an appendicitis model in rats, and antibiotic activity was evaluated by using biochemical and immunohistochemical evaluation.

In the experimental model we used, cecal ligation model was used similar to that established by Elemen because rat appendix was not found as an isolated organ from the cecum [16]. In our study, we established a model suitable for obstruction of appendiceal lumen in rats. The model showed similar results to the clinical course of appendicitis in humans. In some of the experimental animals left alone, the infection was limited, while in others, the results showed widespread infection, such as death of the experimental animal.

Leukocyte values are among the most frequently used biochemical parameters in the diagnosis of appendicitis. It is an important indicator in diagnosis. However, the fact that leukocyte value alone is a diagnostic criterion is not evidence based. In a retrospective study on 227 patients, increased leukocytes indicate a sign of appendicitis [17]. The leukocyte count was used as a clinical follow-up criterion in the treatment of uncomplicated appendicitis only with antibiotic, and the gradual decrease in leukocyte values indicates that the inflammation is benefiting from the treatment. In our study, it is important that the leukocyte counts decreased more in the treatment group (group 3), although there was no statistical difference. Although our results do not support much, the leukocyte count will continue to be a follow-up criterion for the monitoring of acute appendicitis treated with antibiotics. The differences in rat physiology probably may have been prevented us from obtaining more predictable results for leukocyte values. Appendectomy does not appear to affect leukocyte values in appendectomy group (group 4) in our study. The low levels of leukocytes in group 3 compared to group 4 may be a finding indicating the effectiveness of antibiotic therapy.

CRP as an acute phase reactant is a biochemical indicator showing an increase in inflammation status. In a retrospective study on 227 patients with acute appendicitis, CRP levels were observed to be significantly elevated in complicated patients [17]. In a retrospective study on 338 adult patients, the ROC analysis showed that high CRP levels were the best diagnostic predictor for uncomplicated appendicitis, and to distinguish perforated appendicitis from simple appendicitis, the CRP level has > 70 cutoff points, a specificity of 80%, and a sensitivity of 50% [18]. In patients with suspected appendicitis, CRP provides the highest diagnostic accuracy. In our study, CRP levels were decreased in rats in treatment group (group 3). The difference was statistically significant when compared to group 1 and group 2. Antibiotic treatment leads to a marked regression in CRP values. The CRP values on 0 and 2nd days were significantly less in group 4 than

group 3, but the values were similar on the 7th day. Antibiotic treatment significantly reduces CRP and is also as effective as surgery. Therefore, CRP may be a follow-up criterion for antibiotic treatment especially from the 2nd day.

In a prospective study in children, preoperative leukocyte and CRP were tested in children operated with suspicious appendicitis [19]. Although the sensitivity of leukocyte and CRP levels alone is low, the sensitivity of the two tests is very high, and the probability of leukocyte and CRP being normal in pathologically confirmed appendicitis is very low.

Procalcitonin is an inflammatory marker that has not been routinely used in the diagnosis of acute appendicitis but has undergone several investigations to establish the diagnostic value in suspected patients. In some prolonged complicated cases, serum procalcitonin value was found to be increased. Kafetzis, in a study including 212 child patients with appendicitis, demonstrated that a procalcitonin value > 0.5 ng/ml was found to be indicative of perforation or gangrene with 73.4% sensitivity and 94.6% specificity values [20]. Considering the biochemical study as a follow-up criterion, we conclude that procalscitonin values have no meaning in the appendicitis model we have created in our study. Even if antibiotic therapy lowers procalcitonin values in the late period, procalcitonin values are not variable, and low values do not correlate with the presence of inflammation or regression of inflammation. There may be several reasons for this as half-life, etc.

In a systematic review and meta-analysis, CRP, procalcitonin, and leukocyte were compared in terms of acute complicated and uncomplicated appendicitis [21]. According to this study, procalcitonin gives less diagnostic accuracy than CRP and leukocytes for uncomplicated cases and is of much less importance; however, procalcitonin shows a greater diagnostic value in the diagnosis of complicated appendicitis. Appendicitis is an inflammatory process that can be monitored by antibiotics. The decrease in CRP values during this follow-up is another finding suggesting that the course of disease together with other criteria (physical examination, lab, etc.) goes in a positive direction. Antibiotic therapy in preventing inflammation is as effective as surgery in selected cases. In terms of serum leukocyte values which are widely used in clinical follow-up, low values, although not statistically significant, indicate that leukocyte values will be a criterion in the follow-up of antibiotic therapy.

In a prospective study with 211 children, different serum inflammatory agents such as leukocytes, serum CRP, IL-6, TNF-α, acid α1-glycoprotein (α1GP), endotoxin, and erythrocyte sedimentation reaction (ESR) compared the diagnostic value of detecting phlegmonous or perforated appendicitis [22]. Patients were divided to nonsurgical abdominal pain, early appendicitis, phlegmon or gangrenous appendicitis, and perforated appendicitis. In statistical analysis, the number of leukocytes, CRP, and IL-6 was significantly correlated with the severity of appendicitis. The identification of children with severe and complicated appendicitis was supported by IL-6 or CRP but was not supported by leukocytes. As a result, laboratory results should be considered integrated together with clinical evaluation, and CRP and IL-6 serum values provide complementary information to surgeons in distinguishing the necessity of urgent operation.

Appendicitis formation in all three layers caused inflammation in groups 2, 3, and 4 compared to the sham group (group 1). Inflammation in all three histological bowel layers is a finding that shows the validity of the model in our study. In terms of TNF-α and IL-6, which are indicators of inflammation at the mediator level, inflammation decreased significantly in group 3 than group 2. Therefore, in general terms, antibiotic treatment reduces pathological inflammation. Since surgery was performed early, there was no change in the cellular inflammatory criteria in histological sections. Surgery prevented the increase in TNF-α and IL-6 inflammation at the mediator level in group 4. Antibiotic therapy is as effective as surgery in preventing all criteria of pathological inflammation.

It is now known that acute appendicitis has no absolute progressive pathogenesis. Antibiotic therapy applied in the treatment of uncomplicated acute appendicitis leads to regression of appendicitis findings by decreasing the possible luminal obstruction by stretching inflammation. In our study, we evaluated the appendicitis materials in terms of the severity of inflammation in rat experimental appendicitis model, and we also investigated the inflammation severity by looking at the TNF-α and IL-6 tissue distribution which are the mediators of inflammation. We found statistical significance of inflammation at cellular level in rats treated with antibiotics. When we evaluated the results of our study, we found that TNF-α and IL-6 levels decreased immunohistochemically according to the group not receiving antibiotic treatment. We also found that the medullary infusions of the infarction continued when the appendicitis was left to its natural course. Another indication of this condition is that the early-stage mediators of inflammation are low. Antibiotic treatment reduces tissue inflammation mediators. This suggests that one of the mechanisms of action of antibiotic treatment in clinical appendicitis is to reduce tissue inflammation mediators.

Conclusion

Acute appendicitis is still a more surgical disease. Appendectomy has been recognized worldwide, and conservative treatment is not common. Certainly, however, some children may benefit from antibiotics in the early hours when surgery is still controversial. Therefore, acute uncomplicated and early appendicitis may be treated with antibiotics in selected cases, with the consent of the patient, her family, and the surgeon. The patient and his/her family should be given sufficient information about the follow-up protocols, and the options for return to surgery should be explained in a clear and detailed way when no response is obtained. Though we found that CRP levels are useful as follow-up criterion in experimental appendicitis model, clinical studies on the assessment of CRP levels in the course of nonsurgical treatment in the patients with acute appendicitis will reveal out the real effectiveness of this marker. For children with acute appendicitis, prospective and long-term follow-up studies are undoubtedly needed.

Limitations

The main limitation of this study may be that rat as an experimental animal does not have an original appendix, and we were obliged to create an appendicitis model by cecal ligation as it was demonstrated in the literature.

Abbreviations

CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6.

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Authors' contributions

HCD: experimental surgery, data collection, and manuscript writing. HIT: manuscript writing, critical revision, and manuscript submission. FT: biochemical examination and analysis. SA: histopathological examination analysis. CG: study design and critical revision. The author(s) read and approved the final manuscript.

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Availability of data and materials

All of the data and material were stored digitally.

Declarations

Ethics approval and consent to participate

The study design was approved by the Experimental Animal Ethics Committee of the Manisa Celal Bayar University (07 June 2016/77.637.435-34), and ethical rules of international animal experimentation have been followed throughout the study.

Consent for publication

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All the authors have approved the manuscript and agree with submission to your esteemed journal.

Competing interests

The authors declare that they have no competing interests.

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