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CLINICAL OUTCOMES OF NON-OPERATIVE TREATMENT OF SUSPECTED UNCOMPLICATED APPENDICITIS IN CHILDREN

KOMPLİKE OLMAYAN APANDİSİT ÖN TANILI ÇOCUKLARDA AMELİYATSIZ TEDAVİNİN KLİNİK SONUÇLARI

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Abstract

Aim: Non-operative treatment approach is another method used in the treatment of uncomplicated appendicitis, in which the infection in the appendix is suppressed and treated with antibiotics. Our study aims to investigate the clinical outcomes and the risk factors for recurrence in our pediatric patients with suspected uncomplicated appendicitis, who underwent non-operative treatment.

Methods: The medical data of the patients who underwent non-operative treatment with the diagnosis of suspected uncomplicated appendicitis between January 2016 and January 2021 in a tertiary pediatric surgery center were analyzed. Demographic data, treatment process, and clinical results of the patients were recorded. Statistical evaluation was made by comparing the two groups with and without recurrence after non-operative treatment.

Results: The median age of 41 patients whose data were evaluated was 13 (6-17) years. Eight patients (19.5%) had appendicolith. The median duration of IV antibiotic treatment was 4 (3-7) days, and the patients' abdominal tenderness disappeared in a median of 2 (1-4) days. Recurrence developed in 8 (19.5%) patients after a median of 7 (1-14) months after non-operative treatment. It was found that the time to the disappearance of abdominal tenderness was statistically longer in the group that developed recurrence than that in the group that did not (p=0.01).

Conclusions: Our study revealed that appendicolith was not a risk factor for the development of recurrence. The time to the disappearance of abdominal tenderness may be useful for detecting patients at a higher risk of recurrence.

Keywords: appendicitis, non-operative treatment, antibiotic, children

Öz

Amaç: Ameliyatsız tedavi yaklaşımı, apendiksteki enfeksiyonun baskılandığı ve antibiyotiklerle tedavi edildiği komplike olmayan apandisit tedavisinde kullanılan diğer bir yöntemdir. Çalışmamızın amaçları komplike olmayan apandisit ön tanılı çocuk hastalarda ameliyatsız tedavinin klinik sonuçlarının ve rekürrens gelişmesi için risk faktörlerinin araştırılmasıdır.

Yöntemler: Ocak 2016 ve Ocak 2021 tarihleri arasında üçüncü basamak bir çocuk cerrrahisi merkezinde komplike olmayan apandisit ön tanılı ve ameliyatsız tedavi uygulanmış hastaların tıbbi verileri değerlendirildi. Hastaların tanımlayıcı bilgileri, tedavi süreci ve klinik sonuçları kaydedildi. Ameliyatsız tedavi sonrası rekürrens gelişen ve gelişmeyen iki hasta grubunun verileri istatistiksel olarak karşılaştırıldı.

Bulgular: Ortanca yaşı 13 (6-17) yıl olan 41 hastanın verileri değerlendirildi. Sekiz (%19,5) hastada apendikolit vardı. Ortanca IV antibiyotik tedavi süresi 4 (3-7) gün ve hastaların ortanca abdominal hassasiyetlerinin kaybolma süresi 2 (1-4) gündü. Ameliyatsız tedaviden ortanca 7 (1-14) ay sonra 8 (%19,5) hastada rekürrens gelişti. Rekürrens gelişen grupta abdominal hassasiyetin kaybolma süresi diğer gruba göre istatistiksel anlamlı olarak daha uzundu (p=0.01).

Sonuç: Çalışmamız apendikolitin rekürrens gelişimi için risk faktörü oluşturmadığını ortaya koydu. Abdominal hassasiyetin kaybolması için geçen zaman rekürrens gelişimi için yüksek riskli hastaların tespitinde faydalı olabilir.

Anahtar Kelimeler: Apandisit, ameliyatsız tedavi, antibiyotik, çocuk

Introduction

Appendicitis is the most common cause of emergency surgeries of the abdomen in children[1,2]. The risk of having appendicitis in children up to the age of 18 is 2.5%, and one out of every six cases is complicated appendicitis[1,2]. Appendicitis is most common in the second decade of childhood and is more common in males[2]. It is divided into two groups, complicated and uncomplicated, according to the perforation of the appendix[3,4]. The basic approach in the treatment of appendicitis is the surgical excision of the appendix[4]. Another treatment method for uncomplicated appendicitis is the non-operative treatment (NOT) with antibiotics approach, which does not have a standardized protocol yet. While the first clinical results regarding the NOT approach for treating appendicitis in adult patients were published in 1959, the results in children began to be published in the second half of the 90s[5,6]. The positive aspects of the NOT approach in uncomplicated appendicitis are the avoidance of unnecessary surgery and anesthesia and the lower costs compared to the surgical approach. The most frequently criticized aspects are the recurrence rates of 5-37%, the lack of a standard treatment algorithm, and the fact that it is unknown how many of the patients who underwent NOT had appendicitis, since appendicitis is a histopathological diagnosis[7-13].

Our study aims to evaluate the clinical results of the uncomplicated appendicitis cases treated with NOT in our clinic and determine the factors that increase the risk of recurrence.

Materials and Methods

The medical data of the pediatric patients under the age of eighteen who applied to our clinic between January 2016 and January 2021, who were diagnosed with uncomplicated appendicitis and underwent the NOT approach, were retrospectively analyzed. The descriptive information of the patients, the treatment protocol applied, the clinical course in the treatment process, the follow-up period after discharge, the recurrence information, and the histopathological evaluations were examined.

Information about the latest clinical status of the patients was obtained by contacting them by phone. The term suspected uncomplicated appendicitis (SUA) was used as the patients' diagnoses, since the diagnosis of uncomplicated appendicitis was not made after a histopathological evaluation. After evaluations from two experienced pediatric surgeons, the patients were diagnosed with SUA, and NOT was applied. The inclusion and exclusion criteria and the patients' discharge criteria after NOT are shown in Table 1. During NOT, cefazolin (50 mg/kg/day, divided into three doses) or cefazolin and metronidazole (30 mg/kg/day, divided into three doses) were used together as intravenous (IV) antibiotics. After discharge, amoxicillin-clavulanic acid was perorally used for seven days at age-appropriate doses. The definition of recurrent appendicitis in the study is the diagnosis of appendicitis after the relapse of abdominal pain in SUA patients who underwent NOT.

For the study, approval was obtained from the Ethics Committee of Non-Interventional Clinical Studies, dated 5.03.2021 and numbered 109. Informed consent was obtained from the parents of the patients participating in the study.

- *Statistical analysis*

Statistical evaluation was done with IBM® SPSS® Statistics 20.0. We presented categorical variables as frequency (percentage) and continuous variables as median with minimum and maximum values. We used Chi-square test to compare categorical variables between groups and Mann-Whitney U test to compare continuous variables. If the p-value was less than 0.05, the result was considered statistically significant.

Table 1. Inclusion and exclusion criteria for the study and the discharge criteria of the patients

Research Inclusion Criteria
❖ No fever at admission ❖ Localized abdominal tenderness ❖ Appendix MOD ≥ 6 mm ❖ NOT was applied and discharged
Research Exclusion Criteria
❖ Fever at admission ❖ Widespread abdominal tenderness at admission (perforation, diffuse peritonitis, abscess) ❖ Development of fever during NOT ❖ Development of widespread abdominal tenderness during NOT ❖ History of previous abdominal surgery ❖ Administration of antibiotics before NOT ❖ Undergoing an appendectomy during hospitalization during NOT ❖ Use of oral antibiotics for less or more than 7 days after discharge ❖ Re-implementation of NOT
Discharge Criteria of Patients
❖ Ability to tolerate a normal diet ❖ The disappearance of abdominal tenderness on clinical examination

MOD: Maximum Outer Diameter, NOT: Non-Operative Treatment, SUA: Suspected Uncomplicated Appendicitis

Results

Fifty-three patients met the study criteria. Twelve patients were excluded from the study due to insufficient data, treatment incompatibility, and the lack of follow-up information. There was additional disease in four patients (asthma n=3, type 2 diabetes mellitus n=1). Two groups were formed in the study; group A included 33 patients who underwent NOT and did not develop recurrence in the follow-up, and the group B comprised 8 patients who developed recurrence and underwent appendectomy. All patients had right lower quadrant tenderness (McBurney's sing) in the first physical examination. The median age of the study group was 13 (6-17) years, and the percentages of males and females were close to each other. Patients age, gender, weight, time to start antibiotic treatment, white blood cell, diameter of appendix on ultrasound, type of IV antibiotic used, duration of IV antibiotic treatment, time of disappearence of abdominal tenderness, initiation to feeding and duration of hospitalization were evaluated as descriptive features. The descriptive features and the clinical findings of all the patients are presented in Table 2. No statistically significant difference was found between the two groups in terms of descriptive features. When the clinical results between the two groups were compared, it was found that the time of disappearance of abdominal tenderness on physical examination during the application of NOT was statistically significantly longer in the group B than that in the other group ($p = 0.01$). A comparison of descriptive features and clinical results between the two groups is presented in Table 3.

Table 2. Descriptive characteristics and clinical outcomes of the study group

	All patients **n = 41**
Age (years)	13 (6-17)
Gender	
❖ Male	20 (48.7%)
❖ Female	21 (51.3%)
Weight (kilograms)	45 (17-109)
White Blood Cell (cells/microliter)	13700 (2000-22600)
Diameter of appendicitis on ultrasound (millimeters)	7 (6-12)
Fecalitis on ultrasound	
❖ Yes	8 (19.5%)
❖ No	33 (80.5%)
Time to start antibiotic treatment (days) *	2 (1-7)
Duration of IV antibiotic treatment (days)	4 (3-7)
Disappearance of abdominal tenderness (days)	2 (1-4)
Initiation to feeding (days)	2 (1-2)
Duration of hospitalization (days)	5 (3-7)
Type of IV antibiotic used	
❖ Cefazolin	10 (24.3%)
❖ Cefazolin + Metronidazole	31 (75.7%)
Recurrence	
❖ Yes	8 (19.5%)
❖ No	33 (80.5%)
Duration between **NOT and recurrence (months)	7 (1-14)
Follow up period (months) (non-recurrent group)	21 (11-65)
Follow up period (months) (patients with appendicolith)	26 (21-89)

Values are median (minimum-maximum) or n (%).
*Time between the onset of abdominal pain and the initiation of treatment
**Non-Operative Treatment

Table 3. Comparison of descriptive characteristics and clinical outcomes between the two groups

	Non recurrent group n = 33	Recurrent group n = 8	P value
Age (years)	13 (6-17)	11.5 (8-16)	0.5
Gender			
Male	16	4	0.6
Female	17	4	
Weight (kilograms)	45 (17-109)	36.5 (25-54)	0.4
Time to start antibiotic treatment (days) *	2 (1-7)	1.5 (1-3)	0.6
White Blood Cells (cells/microliter)	13000 (2000-22600)	14450 (8100-19600)	0.6
Diameter of appendix on ultrasound (millimeters)	7 (6-12)	8 (6-10)	0.6
Type of IV antibiotic used			
❖ Cefazolin	9	1	0.7
❖ Cefazolin + Metronidazole	24	7	
Duration of IV antibiotic treatment (days)	4 (3-7)	4 (3-7)	0.7
Disappearance of abdominal tenderness (days)	2 (1-4)	3 (2-4)	**0.01**
Initiation to feeding (days)	2 (1-2)	2 (1-2)	0.9
Duration of hospitalization (days)	5 (3-7)	4.5 (3-7)	0.6

Values are median (minimum-maximum)
*Time between the onset of abdominal pain and the initiation of treatment

Discussion

In SUA patients, NOT was performed on 41 patients, and recurrence developed in 8 (19.5%). Recurrence developed a median of 7 (1-14) months after NOT. The time required for the disappearance of abdominal tenderness after the initiation of IV antibiotic therapy during hospitalization was found to be statistically significantly longer in the group with recurrence (p = 0.01).

The median age of the study group was 13 (6-17) years, consistent with the age range where appendicitis is most common in the literature, and the percentage of males in the study group was found to be less (48.7%) than in the literature[2]. The median body weight of the patients was 45 (17-109) kilograms, and Body Mass Index could not be calculated due to the lack of height data. It was found that the patients had applied to our clinic a median of 2 (1-7) days after the onset of abdominal pain. There was no sta-

tistically significant difference between the two groups in terms of the time between the onset of abdominal pain and the initiation of IV antibiotic therapy (p = 0.6). All the patients experienced pain in the right lower quadrant of the abdomen and tenderness at the first examination, but there was no sign of diffuse peritonitis and fever.

White Blood Cell (WBC) elevation has been defined in pediatric patients with appendicitis, and its sensitivity for the diagnosis of appendicitis has been reported as 67-88% and specificity as 53-80%[14,15]. Grönroos stated in his study that 7% of the children with acute appendicitis had normal leukocyte levels[15]. In our study, the median WBC value of the patients at the beginning of the hospitalization was 13700 (2000-22000) cell/mcL, and the WBC value of 20 (48.7%) patients was within normal limits. WBC value was found below the normal limits in one patient at 2000 cell/mcL, and this patient's platelet value was 39000 cell/mcL. This patient was followed up for further hematological examination, and no recurrence developed in this patient.

One of the imaging methods frequently used in the diagnosis of appendicitis in children is ultrasonographic evaluation of the abdomen. It has been published that the sensitivity and the specificity of the ultrasound in the diagnosis of appendicitis are 88% and 94%, respectively[16]. Findings of mesenteric fat stranding, fluid collection, non-compressible appendix, and an appendix diameter over six millimeters in the abdominal ultrasound performed for abdominal pain were defined as compatible with appendicitis[17]. In our study, since only the maximum outer diameter (MOD) of the appendix was regularly reported among the findings supporting appendicitis in the abdominal ultrasound reports, the MOD of the appendix was evaluated in the study. Tanaka et al. found in their study that the mean appendix MOD was 8.5 ± 2.1 mm in the group without recurrence and 9.5 ± 2.3 mm in the group with recurrence, and no statistically significant difference was found between them[8]. In our study group, the median appendix MOD was 7 (6-12) mm, and there was no statistically significant difference between the two groups when the appendix MOD was compared (p = 0.6).

Appendicolith is defined as fecal concentration and is more common in children than in adults[18]. Singh et al. reported that 29.9% of the pediatric patients with acute appendicitis, and 56.1% of those with perforated appendicitis had appendicolith in the appendix. In a prospective non-randomized study examining the feasibility of NOT in children with acute appendicitis in whom appendicolith was detected, 60% of the patients developed recurrence within five months after the application of NOT, and the study was stopped[19]. In another study, the recurrence rate was 47% in the patients with appendicolith, while the recurrence rate was reported as 23.7% in the patients who did not (p = 0.049)[8]. In our study, appendicolith was detected in the appendix by ultrasound in 8 (19.5%) patients, but recurrence did not develop in any of them. The median and range of the follow-up period of these patients were 26 (21-89) months. The reason for this result, which is inconsistent with the literature, may be the duration of the antibiotic use, which was longer in our study than in both of the other studies[8,19].

The published studies state that different antibiotic protocols and durations of use were applied during the NOT. Tanaka et al. used different IV antibiotic protocols, such as sulbactam/ampicillin and ceftazidime or meropenem or imipenem/cilastatin and gentamicin, to increase the probability of success when the success rate after cefmetazole, the first antibiotic used, was 85.7% when applying NOT. They stated that the success rate after the modified antibiotic protocol was 98.7%. However, it has been reported that different antibiotic regimens, such as IV piperacillin/tazobactam and ciprofloxacin/metronidazole, were used in the first treatment[8,11,20]. In some study protocols, IV antibiotics were discontinued after 1-2 doses, depending on the improvement in the clinical condition after hospitalization, while oral antibiotic treatment was

started afterwards[11,20,21]. The pediatric literature has studies in which oral antibiotics are not given after discharge and studies in which oral amoxicillin-clavulanic acid or ciprofloxacin/metronidazole are used[9,11,22].
In our study, 10 (24.3%) patients were given IV cefazolin and 31 (75.7%) patients were given IV cefazolin and metronidazole for a median of 4 (3-7) days while NOT was applied. No statistical difference was found between the groups in the study in terms of the duration and the types of IV antibiotic administration (p = 0.7, p = 0.7). Oral amoxicillin-clavulanic acid treatment was administered to all patients in the study group for seven days after discharge.
In the literature, there is no standardization in the discharge criteria of patients. Tanaka et al. determined CRP < 0.5 mg/dl, absence of fever, and absence of abdominal pain as discharge criteria. However, the absence of fever, decrease or disappearance of pain, and the ability to tolerate feeding were generally used as discharge criteria[8,9,21,23]. The discharge criteria of our study were loss of abdominal tenderness and tolerance to oral feeding. The median duration of loss of abdominal tenderness in our patients was 2 (1-4) days, and the median time to start oral feeding was 2 (1-2) days. The disappearance of abdominal tenderness after starting IV antibiotics was found to be statistically significantly longer in the group B (p = 0.01), while there was no statistically significant difference between the initiation of oral feeding in both groups (p = 0.9). We think that the statistically longer duration of the disappearance of abdominal tenderness on physical examination after IV treatment in the group B may be important data for the early detection of patients who may develop recurrence.
Although few studies in the literature discuss the economic impact of NOT in children with SUA, Mosuka and Wu emphasized that NOT is cost-effective[12,24]. In our study, however, the economic dimension of the treatment was not evaluated.
The hospitalization time of the patients in our study was 5 (3-7) days, and no statistically significant difference was found between the two groups in terms of hospitalization time (p = 0.6).
Abdominal pain may develop in patients discharged after NOT administration. If this abdominal pain is diagnosed as recurrent appendicitis, there are options, such as a new course of NOT treatment or an appendectomy. It is observed that the recurrence rates increase with the prolongation of the follow-up period of the patients. While the one-year success rates are 71-95%, overall success rates have been reported as 62-76%[7,8,21]. In the meta-analysis of Georgiou et al., in which 413 patients were evaluated, the recurrence rate was reported as 14%[10]. When comparing success rates, it should be kept in mind that there is serious heterogeneity between the patients' characteristics, treatment protocols, and follow-up periods in the studies.
In our study, 8 (19.5%) patients who were treated with NOT developed recurrence after a median of 7 (1-14) months, and appendectomy was performed on them. In three patients, NOT was performed for the second time after recurrence, and they were discharged. These patients did not develop recurrence and were not included in the study group. Three patients who developed recurrence and underwent appendectomy were operated on outside of our clinic. The histopathological results of the five patients whose results we reached were reported as acute appendicitis. The median follow-up period of the group A was 21 (11-65) months.
The most important limitations of our study are that it is a retrospective study, it does not include a large cohort, and there is no research on the economic cost of NOT.

Conclusion

In our study, our recurrence rate was 19.5% in SUA patients who underwent NOT. The presence of appendicolith in the appendix on ultrasound was not found to be a risk factor for the development of recurrence. The time between the initiation of IV antibiotics

and the disappearance of abdominal tenderness in the group with recurrence was found to be statistically significantly longer than that in the group without recurrence. We think that this result can be useful in detecting patients who may develop recurrence after NOT. However, the reliability of this data needs to be checked in larger series.

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

Ethical approval was taken from the Cukurova University local Ethics Committee, and the principles of the Declaration of Helsinki had carried out (Document No.05.03.2021/109).

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