Prediction of the outcome of nonoperative management of uncomplicated acute appendicitis in adults

Original Article

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ABSTRACT

Background: Antibiotic treatment may be an effective treatment modality for adult patients with acute appendicitis (AA) and ~75% of those patients may not need appendectomy at all, either during initial illness or during the first year of follow-up.

Aim: This clinical trial aimed to investigate the outcome (success/failure) of nonoperative management (NOM) of uncomplicated AA in adults and to identify the independent predictors of this outcome.

Patients and Methods: A prospective cohort study was conducted at Tanta University Hospitals during the period from July 2021 to July 2022 on 160 adult patients diagnosed with uncomplicated AA. Included patients received IV levofloxacin and metronidazole for 72 h. Daily clinical, laboratory, and ultrasound evaluation was performed. Patients responding successfully to NOM were discharged home while those who failed NOM were subjected to appendectomy.

Results: The study included 81 males and 79 females with a mean age of 27.6 years and a mean BMI of 23.3 kg/m^2. Total 137 (85.6%) patients showed successful outcomes of NOM during the initial admission. Multivariate analysis identified diabetes mellitus and longer duration of symptoms before admission as independent predictors of failure of NOM. During the 6 months follow-up, only two (1.5%) patients in the successful NOM group showed recurrent AA.

Conclusion: NOM with antibiotics in adult patients with uncomplicated AA is associated with a high success rate. diabetes mellitus and longer duration of symptoms before admission were identified as independent predictors of failure of NOM.

Key Words: Appendicitis, predictors, uncomplicated.

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INTRODUCTION

With a lifetime risk of 8.6% for males and 6.7% for females, acute appendicitis (AA) is among the most common causes of acute abdominal pain leading patients to the emergency department[1]. Traditionally, AA is treated with appendectomy by either an open or a laparoscopic approach making appendectomy one of the most frequent surgical procedures[2]. Appendectomy, like any other operation, has potential complications on both short and long-term follow-up including wound infections, ileus, intra-abdominal abscesses, intra-abdominal adhesions, and incisional hernia[3].

There is a growing interest in the nonoperative management (NOM) of uncomplicated AA. Data suggest that antibiotic treatment may be an effective treatment modality for adult patients with AA and that ~75% of those patients may not need appendectomy at all, either during initial illness or during the first year of follow-up[4]. The immune function of the appendix, which may act as a crucial component of gut immunity, is preserved by NOM, and this is why proponents of this course of therapy support it[5].

The lack of high-quality research on the applicability of conservative treatment with antibiotics for uncomplicated AA to the general population in terms of patient-centered outcomes, such as quality of life and overall complication rates, has highly limited the use of this strategy[6]. In a survey study of 1728 respondents, 1566 (90.6%) respondents chose appendectomy, and 162 (9.4%) chose antibiotics alone[7].

Several studies, published in the last decade, support the clinical hypothesis that the presence of an appendicolith is an independent predictor of both perforation and failure of NOM of AA[8,9], therefore, it is strongly recommended to exclude patients with appendicoliths from NOM[10]. Other independent predictors of the outcome of NOM varied among different clinical trials. These included C-reactive protein (CRP) level, white blood cell (WBC) count, age

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of the patients[11], duration of symptoms before admission, body temperature, modified Alvarado score, and diameter of the appendix on imaging studies[12].

PATIENTS AND METHODS:

This prospective cohort study was conducted during the period from July 2021 to July 2022 and included 160 adult patients with uncomplicated AA. The study protocol was approval by the ethical committee of Tanta University Hospitals and informed written consent was obtained from all patients.

Patients with complicated AA (appendicular mass, perforation with abscess formation, or diffuse peritonitis), patients with appendicular fecalith identified on imaging studies, those with suspicion of tumors, those with allergic reactions to antibiotics used in the study, those with a previous history of nonoperative treatment of AA, pregnant or lactating females and patients with severe systemic illness were excluded from our study.

Pre-admission assessment

Selected patients were subjected to history taking physical examination and appropriate laboratory investigations. All patients had abdominal US scan looking for signs of AA, fecalith, peri-appendicular fluid, or complications like appendicular mass or abscess.

Intervention protocol

Patients were admitted to the hospital and received IV levofloxacin (500 mg once daily), IV Metronidazole (500 mg three times daily), and IV Paracetamol (1 g three times daily) for the first 72 h. The visual analog scale (VAS) for assessment of abdominal pain severity was obtained daily and laboratory tests including CRP, and total and differential leucocytic counts (TLC) were repeated daily. Abdominal US scan was repeated before discharge for patients responding successfully to NOM and for patients suspected of developing complications. Success was defined as relief of abdominal pain and improvement of clinical, laboratory, and radiological parameters allowing discharge on oral antibiotics. Failure was defined as aggravation of abdominal pain and deterioration of clinical, laboratory, and radiological parameters mandating the need for appendectomy during hospitalization.

According to the patient's response to medical treatment, one of two strategies was followed:

(a) For patients with successful NOM, treatment was shifted to oral levofloxacin (500 mg once daily) and metronidazole (500 mg three times daily) or clindamycin 300 mg (three times daily) for another 7 days as a home treatment. Criteria for discharge were: afebrile patient for the last 24 h, tolerating oral feeding, no or minimal abdominal pain (VAS < 4) or tenderness, CRP less than or equal to 6 mg/L, and TLC less than or equal to 11 000/all.

(b) Patients with failed NOM, underwent appendectomy. The operative findings explaining failure of NOM were looked for and recorded.

Follow-up after discharge

Patients with successful NOM had follow-up visits in the outpatient clinic 1 week after discharge, then, at 1, 3, and 6 months afterward. During this period, patients who developed recurrent AA underwent appendectomy.

Endpoints

The primary endpoints were the outcome (success/failure) of NOM and the independent predictors of this outcome. The secondary endpoint was the recurrence of AA within the 6-month follow-up period.

Statistical analysis

The sample size and power analysis were calculated using Epi-Info software statistical package created by WHO and the Center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation were a 95% confidence limit and 80% power of the study. The sample size was found at N=100 patients. The collected data were analyzed using Microsoft Excel software. Gathered data were imported into SPSS (Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov–Smirnov test and Shapiro–Wilk tests were used to verify the normality of distribution. Quantitative data were described using range, mean, SD. The significance of the obtained results was judged at the 5% level. The following tests were used to identify the rate of success of NOM of uncomplicated AA and to define the independent predictors of failure of this treatment. The used tests were χ^2 test, Fisher's Exact or Monte Carlo correction, Mann–Whitney test, Friedman test, Student t-test, ANOVA with repeated measures.

RESULTS:

Over the study period, we received 300 patients presenting with AA and 160 patients (53.3%) of them met our selection criteria and were included in the study. The patients' age ranged between 18 and 60 years with a mean of 27.62±8.52 years and 81 (50.6%) patients were males. One hundred thirty-seven patients (137/160, 85.6%) showed successful outcomes of NOM during the initial admission. More than half of the patients who failed NOM, (12/23, 52.2%) were diabetic (DM) and out of the 16 patients with DM, 12 patients (75%) failed NOM and only four (25%) patients responded successfully and this difference was

found statistically significant (*P<0.001*). Patients with successful NOM had a significantly lower BMI, shorter duration of symptoms, lower VAS, and lower pulse rate on admission, after 24 h and after 48 h in comparison to patients with failed NOM (Table 1). The difference in the Alvarado score between patients with successful and failed NOM was statistically insignificant on admission (*P<0.062*), but it was significantly lower (*P<0.001*) at 24 h, and at 48 h.

The difference in the TLC, the neutrophil percentage, the frequency of positive CRP and the level of CRP between patients with successful and failed NOM on admission, at 24 h and at 48 h was statistically significant (*P<0.001*). On U/S examination, signs of AA were significantly more frequent in patients in the failed NOM group in comparison to those in the successful NOM group (*P<0.001*). Similarly, the hospital length of stay (LOS) and time to return to normal activities showed a statistically significant difference between the successful and the failed NOM groups (*P<0.001*) (Table 2).

The univariate logistic regression analysis of several variables revealed that higher BMI, presence of DM, duration of symptoms before admission, tachycardia, higher TLC, higher neutrophil percentage, higher CRP, larger appendicular diameter, presence of peri- appendicular free fluid and enlarged mesenteric lymph nodes were associated with failure of NOM. On multivariate logistic regression analysis, only the longer duration of symptoms prior to admission and DM, were independent predictors of failure of NOM (Table 3).

Table 1: Patients' demographic data and duration of symptoms prior to admission

	Total (*n*=160) [n (%)]	Successful(*n*=137) [n (%)]	Failed (*n*=23) [n (%)]	*P*
Sex				
Male	81 (50.6)	67 (48.9)	14 (60.9)	**0.288**
Female	79 (49.4)	70 (51.1)	9 (39.1)	
Age (years)	27.62±8.52	27.32±8.44	29.39±8.94	**0.182**
BMI (kg/m^2)	23.39±4.51	23.10±4.61	25.13±3.44	**0.009***
Comorbidities				
DM	16 (10.0)	4 (2.9)	12 (52.2)	**<0.001***
Bronchial asthma	14 (8.8)	14 (10.2)	0	
Hypertension	9 (5.6)	9 (6.6)	0	
Duration of symptoms (h)				
<42	128 (80.0)	128 (93.4)	0	**<0.001***
>42	32 (20.0)	9 (6.6)	23 (100.0)	
Mean±SD	33.65±15.62	28.47±9.28	64.52±8.14	**<0.001***

Table 2: Radiological data and hospital length of stay

	Total (*n*=160) [n (%)]	Successful(*n*=137) [n (%)]	Failed (*n*=23) [n (%)]	*P*
Peri-appendicular free fluid	81 (50.6)	62 (45.3)	19 (82.6)	**0.001***
Appendicular diameter (mm)				
<6	37 (23.1)	37 (27.0)	0	**0.004***
>6	123 (76.9)	100 (73.0)	23 (100.0)	
Mean diameter	7.03±0.72	6.88±0.64	7.96±0.47	**<0.001***
Hospital LOS (day)	3.33±0.86	3.0±0.0	5.30±0.76	**<0.001***
Time to return to normal activities (day)	4.76±1.91	4.08±0.82	8.78±1.51	**<0.001***

Table 3: Logistic regression analysis (only variables with statistical significance were reported)

	Univariate analysis	
	OR (95% CI)	*P*
BMI (kg/m^2)	1.096 (1.0–1.201)	**0.049***
DM	4.444 (1.771–11.153)	**0.001***

Duration of symptoms	1.509 (1.159–1.964)	**0.002***
CRP on admission	1.089 (1.043–1.137)	**<0.001***
TLC on admission	1.984 (1.528–2.577)	**<0.001***
Neutrophil % on admission	1.326 (1.177–1.494)	**<0.001***
Pulse on admission	1.271 (1.146–1.408)	**<0.001***
Enlarged mesenteric lymph nodes	21.375 (5.824–78.445)	**<0.001***
Peri-appendicular free fluid	5.746 (1.857–17.778)	**0.002***
Appendicular diameter (mm)	26.330 (7.336–94.497)	**<0.001***
	Multivariate analysis	
	OR (95% CI)	*P*
DM	81.433 (2.510–2642.412)	**0.013***
Duration of symptoms (days)	1.450 (1.150–1.829)	**0.002***

CI, confidence interval; OR, odds ratio.

DISCUSSION

Introduced in 1889, 40 years before the advent of antibiotics, appendectomy is universally considered the gold standard treatment of uncomplicated AA[13]. Nevertheless, NOM appears to be beneficial in uncomplicated AA as evidenced by a high success rate, decreased morbidity, fewer days out of work, and cheaper expenditures when compared with surgery[14,15]. It may be more appropriate, however, to decide which approach is best for a given patient rather than to try proving that operative or NOM of appendicitis is preferable. When NOM is considered for a given patient, the important question is: what is the chance of this patient responding? Independent predictors of failure of NOM of AA have been reported by several investigators. Appendicular fecality is widely believed to be associated with failure of NOM and complicated appendicitis[8,10,16,17]. Other independent predictors of failure of NOM include high CRP level, high WBC count, old age, long duration of symptoms prior to admission, high body temperature, high modified Alvarado score, and large diameter of the appendix on imaging studies[11,12,16,18].

In the current study, 137 patients (137/160, 85.6%) responded successfully to NOM at initial admission. Over the 6-month follow-up period, only two patients (2/137, 1.5%) developed recurrent AA and underwent appendectomy. Since most published clinical trials reported either the 30-day or the 1-year follow-up results, it is difficult, however, to compare this outcome with other results published in the literature.

The largest SR and MA published so far is that of Poddar *et al*. 2019 which included 20 studies; 10 in adults, comparing antibiotic treatment of AA with surgical treatment. A total of 1743 allocated to antibiotic treatment and 1875 to surgical treatment. Antibiotic treatment failure at index admission and the recurrence rate at 1-year were reported in 8.5% and 19.2%, respectively. Higher complication-free success rate (82.3% vs. 67.2%; *P<0.00001*) and treatment efficacy based on a 1-year follow-up rate (93.1% vs. 72.6%; *P<0.00001*) were reported for surgical treatment. The authors concluded that antibiotic therapy could represent a feasible treatment option for image-proven uncomplicated AA, although complication-free treatment success rates are higher with surgical treatment[19].

A recent SR and MA was published by Harrod *et al*. 2022 of eight RCTs including 3203 participants (1613 antibiotics/1590 appendectomy). NOM had a reduced efficacy compared with appendectomy in controlling uncomplicated AA. In 1 year, NOM was only successful in 1016 of 1613 (62.9%) participants with a six-fold increase in hospital readmissions[20]. The high success rate observed in the current study can be explained by the strict selection criteria excluding patients with complicated AA, those with an appendicolith identified on preoperative imaging, patients with suspicion of a tumor on the preoperative imaging, and patients with previous nonoperative treatment of AA.

In the current study, multivariate logistic regression analysis identified the longer duration of symptoms before admission and DM, as independent predictors of failure of NOM. Different predictors of failure of NOM have been reported in different studies. In the study by Vons *et al*., risk factors for failure were fever at initial presentation, high presenting serum CRP levels, and an intraluminal appendicolith[17]. The combination of elevated levels of CRP and an appendicolith predicted the failure of antibiotic therapy in the study of Shindoh *et al*.[16]. Hansson *et al*., suggests that a combination of a serum CRP less than 60 mg/l, a

WBC less than 12, and age younger than 60 years can provide a very good chance of successful NOM[11]. Wakasa *et al*., reported that elevated CRP level, the presence of fecal stones, and suspected fluid collection were independently associated with NOM failure on multivariate analysis[21]. Moreover, Kobayashi *et al*., reported that male sex, maximal diameter of the appendix, and the presence of appendicolith were identified as independent predictors of NOM failure for uncomplicated AA[22].

Many of the previously mentioned studies and others found that the presence of appendicular fecality on imaging was an independent predictor of NOM failure; that is why we excluded patients with appendicolith identified on preoperative imaging from our study. Interestingly, 6 patients of the 23 (26%) patients who failed NOM in the current study had appendicolith on histopathological examination of the resected appendices after appendectomy. It is clear that megaliths found in these six patients were missed on preoperative US, and this finding highlights the insensitivity of US and suggests that a more accurate imaging study, like a computed tomography scan, may be needed before considering a certain patient with AA for NOM.

Thirty-nine (24.4%) patients in our study had comorbidities, 16 (10%) patients were DM. Out of the 23 patients who failed NOM, 12 (52.2%) patients were DM. Moreover, 12 out of the 16 (75%) patients with DM failed NOM and only four (25%) patients responded successfully to NOM and this difference was found statistically significant (*P<0.001*). Tsai *et al*. 2017, found that women with DM showed a significantly higher failure rate of NOM[23].

The main limitation of this study is the short follow-up period of 6 months. The longest-term follow-up period published so far was 4 years[24]. In this report, more than 80% of all recurrences were recorded during the first year. So, it is important to maintain follow-up for at least 1 year after intervention to identify the recurrence rate more accurately.

CONCLUSION

We conclude that NOM with antibiotics is associated with a high success rate in patients with uncomplicated AA. At initial admission, 137 out of 160 (85.6%) patients responded successfully to NOM, while 23 (14.4%) patients failed to respond. The overall 6-month success rate decreased to 84.4% after a recurrence of AA mandating appendectomy in two patients. DM and longer duration of symptoms before admission were identified as independent predictors of failure of NOM.

CONFLICT OF INTEREST

There are no conflicts of interest.

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