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ORIGINAL ARTICLE

Never put equipoise in appendix! Final results of ASAA (antibiotics vs. surgery for uncomplicated acute appendicitis in adults) randomized controlled trial

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Abstract
Acute appendicitis is the most common surgical emergency; however, its etiology and diagnosis are still discussed with a considerable proportion of wrong diagnosis resulting in appendectomies for non inflamed appendix. Moreover, the biologic function of the appendix is still unclear. For uncomplicated acute appendicitis the conservative treatment with antibiotics has been proposed with interesting results. The aim of this study was to compare surgical treatment vs. antibiotics in uncomplicated acute appendicitis. This is a monocentric randomized controlled trial comparing surgery with antibiotic therapy in adults with uncomplicated acute appendicitis. The primary outcome was the success rate (resolution of symptoms within 2 weeks and no need for further treatments); secondary outcomes were complication rate; negative appendectomy rate (only in surgical arm); and long-term outcomes within a year as recurrence. The study was designed as a non-inferiority trial. From September 2011 to December 2014, 224 patients fulfilled the eligibility criteria and 45 patients were randomized. Twenty four patients (53.3%) were randomly assigned to surgery and 21 (46.6%) to antibiotic therapy. In surgical group primary outcome was reached for all the patients; secondary negative outcomes were recorded in five patients (22.7%): two cases of negative appendectomies, three wound infections. In antibiotics group treatment fails in 16.8% of cases; secondary negative outcomes were recorded in one patient who experienced relapse of AA at 30 days No further events or complications were observed at 1-year follow-up. Due to the poor patients' accrual the study had no enough statistical power to demonstrate the non-inferiority of conservative treatment and results were inconclusive. Due to the poor patient's accrual rate the study failed to demonstrate the non-inferiority of conservative treatment in uncomplicated acute appendicitis. On the other hand the study demonstrates the difficulty in performing randomized trials in emergency surgery and focus on the ethical aspects.

Keywords Acute appendicitis · Uncomplicated acute appendicitis · Conservative treatment · Antibiotics · Equipoise · Randomized trial

> "We're neither better nor worse than each other, we're an equipoise in difference-but in difference, mind, not in sameness".
>
> D. H. Lawrence, "Education of the People", Reflections on the Death of a Porcupine and Other Essays, 1925

Introduction

Acute appendicitis is one of the most common surgical emergencies with an incidence of 90 cases/100,000 inhabitants per year [1]. Despite appendectomy was one of the first emergency surgery intervention described in history, with the first publication in the late nineteenth century [2, 3], the exact etiology of acute appendicitis remains currently unclear. With multiple clinical patterns and a very heterogeneous presentation, the diagnosis of acute appendicitis remains a very difficult "clinical" diagnosis even for most experienced surgeons, with a reported rate of negative appendectomy (a histopathological diagnosis of normal appendix) ranging from 6 to 20% [4, 5].

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Historically the diagnosis of acute appendicitis was based on right iliac fossa tenderness with the McBurney's sign, fever, nausea and vomit. As the accuracy of these signs and symptoms in diagnosing acute appendicitis is weak, several diagnostic scores have been proposed to improve accuracy. One of the most precise and accurate is the appendicitis inflammatory response (AIR) proposed by Andersson [6], developed modifying the more widely used Alvarado score [7]. The AIR score, combining sign and symptoms, divides patients into three groups: low risk, intermediate and high risk of having acute appendicitis. This score has been validated in several studies with good diagnostic performance and allows to identify patients with acute appendicitis who will likely benefit from surgical intervention and patients with an intermediate probability, for whom a conservative treatment should be considered.

An increasing number of studies are describing two different entities of acute appendicitis, being represented by complicated and uncomplicated appendicitis [8–11]. For complicated appendicitis (e.g., peritonitis and perforation), surgery is mandatory. On the other hand, several studies, including randomized trials and meta-analysis, have addressed safety, effectiveness, therapeutic appropriateness and cost-efficiency of antibiotic treatment [12–19]. All these studies (in large part published after the conception of ASAA study) demonstrated that conservative treatment is a safe and a valid option, although associated with a considerable recurrence rate. Moreover, a recent randomized trial shows that uncomplicated appendicitis could resolve spontaneously even without antibiotics [20].

The rationale for conservative treatment in uncomplicated acute appendicitis is to avoid a surgical intervention in a considerable high proportion of patients who present with a clinical suspicion of acute appendicitis. It is worth mentioning how numerous aspect of appendiceal physiology remain unclear and this elements acquires importance when preservation is discussed. Vermiform appendix should not be considered merely as a vestigial organ; in fact its fundamental role in immunoregulation of the gastrointestinal tract and maintenance of the gut microbiota has been demonstrated; moreover, it seems to play a relevant role even in inflammatory bowel diseases [21].

The aim of this study was to test the equivalence of antibiotics versus appendectomy in a population with an intermediate diagnostic risk of uncomplicated acute appendicitis, as per AIR score stratification, to reduce the rate of negative appendictomies.

Materials and methods

ASAA study was conceived as a monocentric prospective randomized non-inferiority trial, comparing antibiotic treatment with surgery in uncomplicated acute appendicitis.

The trial was reviewed and approved by the ethic committee and it has been registered on ClinicaTrial.gov (ClinicalTrials.gov identifier NCT01421901, EUDRA CT number 2011-002977-44). The study was conducted at the Papa Giovanni XXIII Hospital, Bergamo, Italy from September 2011 and was terminated in December 2014.

Patients and eligibility criteria

Patients aged 18–65 years with a first episode of uncomplicated acute appendicitis were considered for inclusion in the study. Exclusion criteria were: complicated AA, on-going immunodeficiency status, active neoplasm or neoplasm in the last 5 years, assumption of antibiotics in the previous 30 days, pregnancy or delivery in the previous 6 months, ASA IV and V, allergy to the antibiotics established for the study.

Diagnosis of AA was made according to the appendicitis inflammatory response (AIR) score [6] with the adjunct of ultrasound in selected patients. According to the AIR score and the ultrasound findings, patients were stratified in three classes as follows. Group 1: AIR score 1–4 (low probability of AA); Group 2: AIR score 5–8 (intermediate probability of AA) and Group 3: AIR score 9–12 (high probability of AA). Patients of group 1 were excluded from the study due to the low probability to have AA. Patients of Group 2 were examined with abdominal US and were included in the study if the US findings confirmed the clinical suspect of AA. Patients of Group 3 without signs of perforation and with white blood cell (WBC) count less than 15,000/μl and C reactive protein (CRP) less than 5 mg/dl were included in randomization; the other were excluded from the study and were operated.

Randomization and masking

Randomization through a computer system was adopted to assign patients in a 1:1 ratio to the two study arms. The randomization list was prepared by a professional not directly involved in the study before the first enrolment and concealed inside opaque envelopes in the surgeon-on-call room. After the evaluation for eligibility, made by the on-call surgeon, and the stratification according to the AIR score and US examination, patients were required to

sign the informed consent for inclusion in the study; at this point the on-call surgeon opened the envelope allocating the patient. For obvious reasons, the current study could not be masked and blinded, neither to the participants nor to the surgeons.

Procedures

Patients who fulfilled the inclusion criteria and gave consent to participate in the study were randomized to either of the two study arms: conservative treatment or surgery.

Conservative treatment consisted of intravenous administration of 1 g of Ertapenem once a day for 3 days during hospitalization and further administration of amoxicillin/clavulanate 1 g per os every 8 h for 5 days. During the hospitalization, the daily AIR scoring was repeated to evaluate a possible failure within the antibiotic arm. A follow-up colonoscopy (after 1 month) was always recommended for all patients older than 40 years, who were managed with conservative treatment.

The surgical arm consisted of preoperative intravenous administration of 1 g of Ertapenem and appendectomy in the following 12 h. Appendectomy was performed routinely laparoscopically, with the standard 3-port approach; open appendectomy was indicated in selected cases, based on the on-call surgeon's choice. In case of phlegmonous or gangrenous acute appendicitis identified at the time of operation, Ertapenem 1 g intravenously daily was administered for 2 further days, followed by Amoxicillin/Clavulanic acid 1 g per os three times per day for 5 days.

For all patient, oral intake was resumed after 12 h after the operation or from the first administration of Ertapenem and patients were allowed to have clear fluids and low fluids diet. Criteria for discharge were ability to tolerate a low fiber diet, passage of flatus, absence fever, optimal pain control with oral medications; and only in the antibiotic group AIR score below 5. All patients were re-evaluated as outpatients after 7 and 14 days from the treatment. Telephonic follow-up was done after 1 year from the acute episode.

Outcomes and dropout

The primary outcome of the study was the success rate of the treatment, defined as the resolution of symptoms (no abdominal pain, no fever) and resolution of inflammatory markers (WBC < 10,000/µl and CRP < 1 mg/dl) within 2 weeks from the appendectomy (in the surgical arm) or from the third dose of Ertapenem without other treatments (in the antibiotic arm).

In the antibiotic arm, primary outcome was considered as not reached if clinical conditions had worsened during the antibiotic administration or if no resolution of symptoms after the third dose of Ertapenem was seen, with the subsequent need for surgical interventions.

Secondary negative outcomes were: complication rate; negative appendectomy rate (only in the surgical arm) and long-term negative outcomes within a year (surgical re-operation due to bowel occlusion or intraperitoneal abscess, bowel occlusion longer than 48 h, intraperitoneal abscess, incisional hernia or wound dehiscence for surgical arm; recurrence of AA in the antibiotic arm). Length of hospital stay and work absence were also compared.

Drop out occurred in the antibiotic group when a different disease was diagnosed during the hospital stay or at the follow-up colonoscopy or when patient refused the participation in the trial after randomization. In the surgical arm drop out occurred when generalized peritonitis and perforations or different diseases were detected during surgery or at the pathological report (except normal appendix) and when patient refused the participation after randomization.

Sample size and statistics

The sample size calculation was based on the outcomes of the most recent prospective trial in the Literature at the time of the study design [12]; we considered an estimated failure rate of 15.1% and 15.2% for antibiotics and surgery, respectively.

To establish the non-inferiority of antibiotic therapy to surgery, we obtained a sample size of 218 patients, 109 patients per treatment arm, considering a power $(1 - \beta)$ of 80% and a type I error risk (α) of 5%, with a non-inferiority margin set at 12%. Taking into account a 10% loss at follow-up, a total number of 230 patients (115 per group) was considered as the enrolment goal of the study.

Data were prospectively collected and entered in an electronic database; continuous variables were expressed as mean and standard deviation; categorical data were expressed as proportion and percentages; primary and secondary outcomes were showed as risk difference with 95% confidence intervals and were compared with non-inferiority test; length of stay and number of sick leave days were compared with the Mann–Whitney test. Data were analyzed with SPSS 20; alpha was set as 0.05.

Results

From September 2011 to December 2014, 366 patients with suspected diagnosis of AA were admitted to the XXXXXXXXXXXXXXXX of these, 224 patients (61.20%) met the inclusion criteria for the randomization. All patients were asked to participate in the ASAA study and the informed consent was obtained for 45 patients that were randomized (45/224, 20.08%). Table 1 shows the main

Table 1 Characteristics of randomized and not randomized patients

	Eligible not randomized patients	Randomized patients	*p*
n	224	41	
Age	38 (15.79)	35.12 (13.35)	0.12
Sex			0.84
Male	120 (54%)	23 (56%)	
Female	104 (46%)	18 (44%)	
AIR score	6 (1.38)	7.37 (1.15)	0.09
Low risk	0	0	
Intermediate risk	206 (92%)	35 (85%)	
High risk	18 (8%)	6 (15%)	

characteristics of randomized and non-randomized patients. Male patients were 23 (51.1%), the mean age was 35.1 years (± 13.3). Twenty four patients (53.3%) were randomly assigned to surgery and 21 (46.6%) to antibiotic therapy. Four patients, two in each group, dropped out: in the surgical group appendiceal perforation was the cause of the dropout in both cases; in the antibiotic group one patient reconsidered his participation during the first day of treatment and one patient was diagnosed with appendiceal carcinoid tumor (well-differentiated pT2), which was detected at histopathology—the appendectomy was performed because no resolution of symptoms was appreciated after the third Ertapenem administration. Patients' flow is shown in Fig. 1. Table 2 shows the characteristics of randomized patients.

Surgery was performed after a median interval time from hospital presentation of 22 (8.3) h. All the appendectomies were successfully accomplished with standard 3-port laparoscopy and no intraoperative complications were recorded. Primary outcome was reached for all the patients, since surgical treatment was effective in 100% of cases; secondary negative outcomes were recorded in five patients (5/22, 22.7%): two cases of negative appendectomies (2/22, 9.1%), three cases of wound infections (3/22, 13.6%). No further complications or events were recorded at 1-year follow-up.

In conservatively treated patients, primary outcome has been reached in 16 out of 19 patients (84.2%). Primary failure, i.e., no resolution/worsening during antibiotic treatment, occurred in three cases and surgery was required. One patient showed worsening of symptoms between the first and the second Ertapenem administration and was operated on with no complications; one worsened between the second and the third Ertapenem administration and at operation was found to have complicated appendicitis (perforation), while the third patient worsened after the third dose of antibiotic.

Secondary negative outcomes were recorded in one patient (1/16, 6.2%), who experienced relapse of acute appendicitis at 30 days from the third dose of Ertapenem:

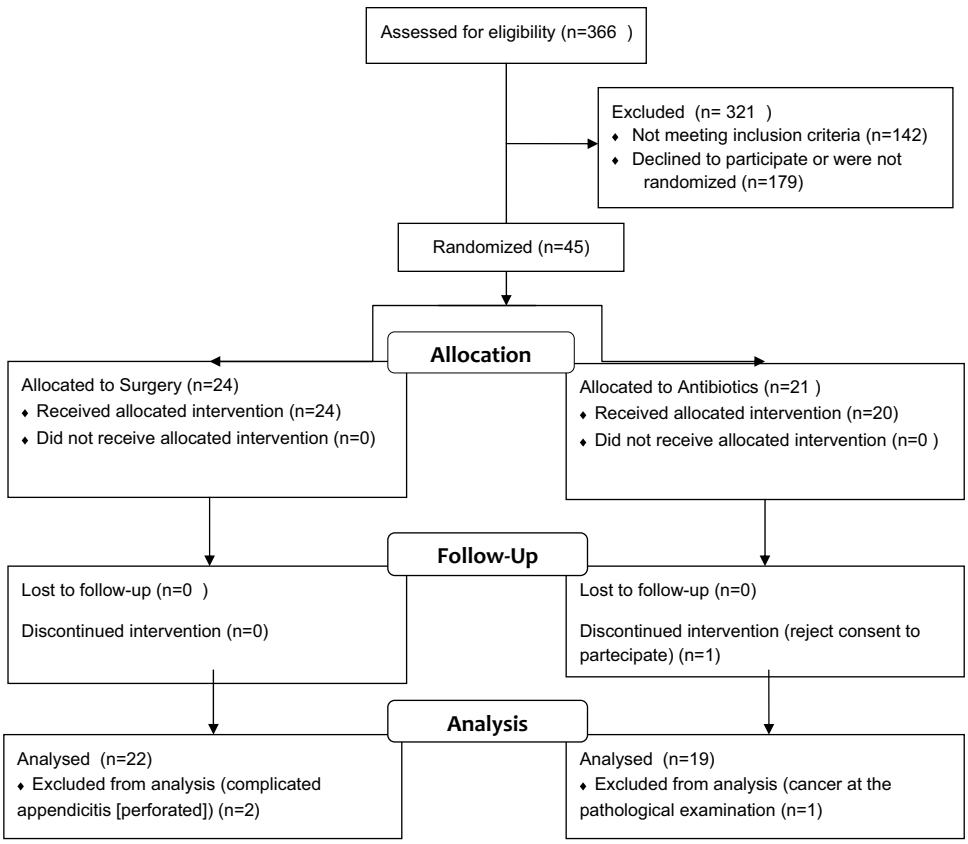

Fig. 1 CONSORT flow diagram

Table 2 Characteristics of included patients among the two study groups

Clinical characteristic	Surgical group	Antibiotic group	*p* value
Number of patients	22	19	
Sex			0.12
Male	14	7	
Female	8	12	
Age	33.6 (±13.2)	37.1 (±13.5)	0.11
AIR score	7.5 (±1.2)	7.2 (±1)	0.48
Low risk	0	0	
Intermediate risk	18 (81%)	17 (89%)	
High risk	4 (19%)	2 (11%)	
RLQ pain presence	24 (100)	19 (100)	0.99
Vomiting presence (percentage)	8 (36.4)	3 (15.8)	0.13
Rebound tenderness presence (percentage)	22 (100)	18 (94.7)	0.79
Absence	0	1 (5.2)	
Blumberg sign	8 (36.4)	7 (36.8)	
Defense at the palpation	10 (45.4)	9 (47.3)	
Abdominal contraction	4 (18.2)	2 (10.5)	
Fever > 38 °C	1 (4.5)	0	0.47
WBC count	14.7 (±3.1)	12.9 (±3.1)	0.12
< 10,000	1 (4.5)	4 (21)	
> 10,000	11(50)	11(57.9)	
> 15,000	10 (45.4)	4 (21)	
% Neutrophil	77.4 (±7.9)	79.3 (±7.9)	0.42
< 70%	4 (18.2)	3 (15.8)	
70.1–84.9%	14 (63.6)	10 (52.6)	
> 84.9%	4 (18.2)	6 (31.6)	
CRP mg/dl	3.5 (±4.1)	5.4 (±5.5)	0.19
< 1.4	7 (31.8)	5 (26.3)	
1.4–4.9	10 (45.4)	7 (36.8)	
> 4.9	5 (22.7)	7 (36.8)	
US	18 (81%)	17 (89%)	0.57

according to the protocol, he underwent surgery and an uneventful laparoscopic appendectomy was performed; no complications were observed. No further events or complication were observed at 1-year follow-up. Table 2 shows the results in detail.

Due to the poor patients' accrual, the study did not present enough statistical power to demonstrate non-inferiority of conservative treatment as shown in Fig. 2 and Table 3; results are, therefore, to be considered as inconclusive.

Discussion

The present study failed to demonstrate the non-inferiority of conservative treatment of uncomplicated acute appendicitis, as compared with surgical treatment. The results obtained from the randomization of patients revealed that conservative treatment failed in 15.8% of cases immediately and in 5.2% within 1 year; on the other hand,

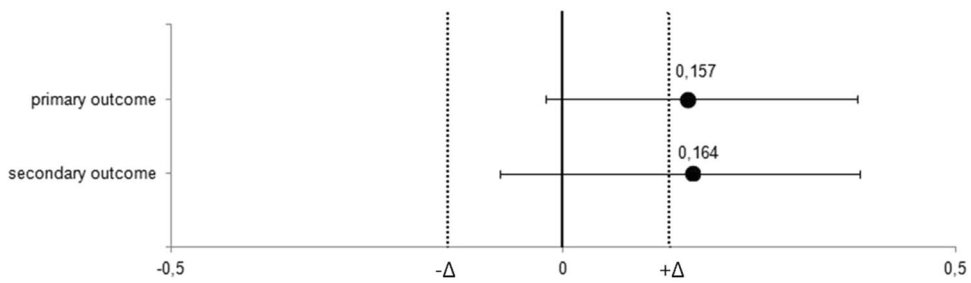

Fig. 2 Risk difference among the two study groups for primary and secondary outcomes; Δ indicates the non-inferiority margin

Table 3 Study's outcomes

	Surgical group	Antibiotic group	Risk difference
Primary outcome	22/22 (100%)	16/19 (84.2%)	0.157 (− 0.022 to 0.375)
Secondary negative outcome	5/22 (22.7%)	1/16 (6.2%)	0.164 (− 0.08 to 0.378)
Length of hospital stay days, mean (SD)	3.5 (± 1.3)	4.1 (± 2.8)	
Sick leave days, mean (SD)	11.4 (± 5.3)	8.5 (± 7.9)	

surgical treatment, with 100% of immediate effectiveness, was inappropriate in two cases (negative appendectomy, 9.1%) and was associated with complication in three cases (13.6%). Due to the poor recruitment of patients, data are far from the needed sample size to demonstrate the non-inferiority of conservative treatment and no statistically valid conclusions can be drawn by the results. It should be noticed that these results seems to be comparable with data available in the literature [18, 19] and they could be considered for inclusion in future meta-analysis.

Although the poor intrinsic statistical results, some general considerations can de proposed: the safety of patients enrolled in the ASAA study was preserved in both arms. No fatal cases have been observed, while the literature refers a range between 0.07–0.7 and 0.5–2.4% in patients without and with perforation, respectively [11]. The overall complication rate reached 9.7% and this was comparable with results in literature; in particular: three were wound infection (first class Clavien–Dindo classification) in the surgical group and one was a atrial flutter (second class Clavien–Dindo classification) in one patient who failed the antibiotic approach. Patients who failed the antibiotic treatment during the hospital stay (15.8%) were able, in any case, to reach the resolution of symptoms at 2 weeks.

The failure of this study allows us to develop some interesting considerations regarding ethical and practical issues when performing RCT in emergency surgery. In 1996 only the 7% of original published papers, in a group of major surgical journals, were RCT [22] and only 40% of questions regarding surgical treatment could be answered by RCT [23]; more recently, these figures have considerably improved, but the quality of evidence is still below the level of RCT comparing medical treatments.

Limiting our analysis to the reasons of insufficient recruitment, we ought to underline the matter of equipoise, which "refers to uncertainty among groups of experts who honestly disagree which treatment is better" [23–26]. The baseline assumption should be that personal certainty among researchers must be abandoned in favor of evidence-based medicine before study conception; subsequently the importance of preserving the equipoise from external influences during the study should be stressed. Factors affecting the maintenance of the researcher equipoise may be different: patient's preference could impair the balance between arms; conflict of interest, either pecuniary (industry funding for devices) or professional (improving personal surgical skills or reluctance to perform a well know surgical operation, especially out-of-hours), could influence the equipoise. In our study, barring the economic influence, each of the cited problems may have contributed to limit the recruitment. A large number of patients, despite being eligible for the study, were excluded for the scarce adherence of the surgeon in charge to the study protocol. Perhaps the main reason for failure of this study is the poor familiarity with RCT among surgeons.

The present study presents the great limitation of a poor patient recruitment rate: an insufficient number of patients was included in the study and the endpoint could not be reached. Moreover, the results revealed the difficulties in conducting a randomized trial in emergency surgery during daily practice. Although the study protocol established a maximum of 12 h from randomization to surgery, patients were operated after a mean time of 22 h, with a very poor adherence to study protocol.

Conclusions

In conclusion, the dogmatic indication to surgery in case of suspected acute appendicitis allowed saving many lives in pre-antibiotic era. However, this approach has decreased the stimulus to investigate the role of the vermiform appendix, to understand the primum movens of acute inflammation of the appendix, to reach a broad agreement on the diagnosis and on the diagnostic tools, to establish a common histopathological classification and to find a worldwide accepted definition of uncomplicated and complicated acute appendicitis.

Unfortunately, the present study does not add further evidences on this intricated topic; however, it demonstrates the great difficulty in providing evidence-based answers to questions directly arising from daily surgical practice.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Research involving human participants and/or animals The study was conducted according to the Helsinki declaration about ethical standards; the study protocol was approved by the etical committee of the Papa Giovanni XXIII hospital.

Informed consent Informed consent to partecipate was obtained from each patient.

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