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Original Article

Role of delay and antibiotics on PERForation rate while waiting appendicECTomy (PERFECT): a protocol for a randomized non-inferiority trial

K. Jalava [1], V. Sallinen[1,2], H. Lampela[1], H. Malmi[1], A. Leppäniemi[1] and P. Mentula [1,*]

[1]Department of Gastroenterological Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[2]Department of Transplantation and Liver Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

*Correspondence to: P. Mentula, Gastroenterological Surgery, Helsinki University Hospital, P.O. Box 340, 00029 HUS, Helsinki, Finland (e-mail: panu.mentula@hus.fi)

Abstract

Background: Longer duration from symptom onset is associated with increased risk of perforation in appendicitis. In previous studies, in-hospital delay to surgery has had conflicting effects on perforation rates. Although preoperative antibiotics have been shown to reduce postoperative infections, there are no data showing that administration of antibiotics while waiting for surgery has any benefits. The aims of this study are to evaluate the role of both in-hospital delay to surgery and antibiotic treatment while waiting for surgery on the rate of appendiceal perforation.

Methods: This prospective, open-label, randomized, controlled non-inferiority trial compares the in-hospital delay to surgery of less than 8 hours *versus* less than 24 hours in adult patients with predicted uncomplicated acute appendicitis. Additionally, participants are randomized either to receive or not to receive antibiotics while waiting for surgery. The primary study endpoint is the rate of perforated appendicitis discovered during appendicectomy. The aim is to randomize 1800 patients, that is estimated to give a power of 90 per cent (χ^2) for the non-inferiority margin of 5 percentage points for both layers (urgency and preoperative antibiotic). Secondary endpoints include length of hospital stay, 30-day complications graded using Clavien–Dindo classification, preoperative pain, conversion rate, histopathological diagnosis and Sunshine Appendicitis Grading System classification.

Discussion: There are no previous randomized controlled studies for either in-hospital delay or preoperative antibiotic treatment. The trial will yield new level 1 evidence.

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Introduction

Worldwide, appendicitis remains one of the most common causes of an acute abdomen in adults and appendicectomy is one of the most frequently performed emergency surgeries[1,2]. The clinical classification into uncomplicated (non-perforated) and complicated (perforated) appendicitis is used to describe the severity of the infection. For perforated appendicitis, there is a strong agreement on urgent appendicectomy. There is no consensus on the urgency of appendicectomy for uncomplicated or non-perforated appendicitis. In large series, perforation at appendicectomy has been observed in 15–22 per cent of patients who were thought before surgery to have non-perforated appendicitis[3–5]. Particularly for this group of patients, it is important to determine whether the in-hospital delay to surgery or antibiotic treatment influence perforation rate .

Several studies have investigated the association of in-hospital delay and risk of perforation in these patients, but the results have been conflicting[6–13]. A large meta-analysis based on retrospective studies demonstrates that delaying appendicectomy for up to 24 hours is safe for patients with no preoperative signs of complicated appendicitis[7]. On the contrary, lengthened in-hospital delay was associated with elevated risk of perforation in patients with appendicitis assumed before surgery to be uncomplicated in a recent large retrospective series[8]. It seems that mild appendicitis does not progress to perforation in most patients and even spontaneous resolution with or without antibiotics has been demonstrated[3,4,14–16].

The guideline recommendations vary in uncomplicated acute appendicitis. Two guidelines recommend to operate on acute appendicitis as soon as feasible[17,18], while World Society of Emergency Surgery (WSES) guidelines recommend to plan laparoscopic appendicectomy for the next available operating list within 24 hours whilst minimizing the delay wherever possible[19]. Currently the daily clinical practice has huge variation between countries, and even within countries, as some hospitals carry out night-time appendicectomies for predicted uncomplicated appendicitis, while others do not. All retrospective series are biased

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as sicker patients are more likely to be operated on sooner than patients with mild symptoms. This selection will inevitably lead to results favouring longer delay.

Even though uncomplicated appendicitis can be managed without surgery, the effect of antibiotics on the perforation rate while waiting for appendicectomy has remained unclear. The infection in appendicitis is caused by intestinal bacteria, therefore it is assumed that antibiotics given before surgery could decelerate the disease's evolution to gangrene and further to perforation. In that case, antibiotic treatment could benefit patients with an increased risk of developing complicated appendicitis. Most guidelines recommend preoperative antibiotics to start as soon as acute appendicitis is diagnosed[17,20] while other guidelines do not define the timing of preoperative antibiotics[18,21]. Recently updated WSES guidelines as well as The Surgical Infection Prevention Guideline Writers Workgroup recommend the administration of a single dose of broad-spectrum antibiotics within 60 minutes before incision[19,22]. Again, the use of antibiotics while waiting for appendicectomy for uncomplicated appendicitis varies hugely between hospitals due to lack of evidence.

The aims of this randomized controlled trial (PERFECT) are to evaluate the role of both delay to surgery for predicted uncomplicated appendicitis, and antibiotics while waiting for surgery, on the rate of appendiceal perforation.

Methods/design

Hypothesis

This study has two hypotheses: first, that longer in-hospital delay is not inferior to shorter delay, and second, that waiting for appendicectomy without antibiotics is not inferior to waiting with antibiotics in patients with predicted uncomplicated appendicitis.

Patient evaluation and selection

Patients are recruited in two hospitals (Meilahti and Jorvi hospitals) at Helsinki University Hospital District in Finland. Patients who have been diagnosed with acute appendicitis and are aimed to be operated upon, are eligible for the study. Acute appendicitis can be diagnosed clinically or by imaging. Patients with high clinical suspicion of acute appendicitis can be diagnosed without imaging by using Adult Appendicitis Score (AAS) (16 or higher)[23]. Acute appendicitis can also be diagnosed by using ultrasonography, CT, or MRI. Before randomization, diagnostic imaging (CT/MRI) should be performed on all patients who have had symptoms for over 3 days to rule out complicated appendicitis[24]. Patients with suspicion of complicated appendicitis based on high plasma C-reactive protein level (CRP) (100 mg/l or greater)[8], high body temperature (over 38.5°C), signs of complicated appendicitis on imaging studies, or clinical generalized peritonitis are excluded from the trial.

Inclusion criteria

All patients with clinically diagnosed appendicitis or appendicitis confirmed by imaging (ultrasonography/CT/MRI) that is aimed to be operated on are included.

Exclusion criteria

- Patients are excluded if they have imaging-confirmed complicated appendicitis (perforation or abscess). Appendicitis is defined as complicated if any of the following radiological findings is present: extraluminal air or extraluminal appendicolith, fluid collection, abscess or phlegmon near to appendix, or an unenhanced appendix (or part of it). They are also excluded if there is a suspicion of complicated appendicitis based on the preoperative laboratory examinations, defined as plasma CRP 100 mg/l or higher[8,25], or clinical generalized peritonitis or other reason requiring an urgent operative intervention.
- Other exclusion criteria are pregnancy; age less than 18 years or over 100 years; no written consent; an allergy to cephalosporin or metronidazole or previous anaphylactic reaction to penicillin or other contraindication for metronidazole (only for the antibiotic layer); the patient is a known carrier of multiresistant bacteria species (only for the antibiotic layer); or antibiotic treatment started before randomization (only for the antibiotic layer).

Randomization

The trial consists of two layers: urgency of surgery and antibiotic treatment while waiting for appendicectomy (*Fig. 1*). Patients participating in the trial are randomized twice. First, eligible patients are randomly allocated (1 : 1) to appendicectomy either within 8 hours or within 24 hours from randomization. Subsequently, the patients randomized to either arm of urgency will undergo a second randomization (1 : 1) either to receive antibiotics whilst waiting for surgery or not to receive antibiotics during the waiting period. Patients who have exclusion criteria that apply only to the antibiotic layer will not undergo the second randomization but will undergo the first randomization for urgency. These patients that do not participate the antibiotic layer of the trial will not get antibiotics unless started earlier for another indication. In that case the antibiotics continue as prescribed.

The randomization sequence is generated using a R statistical software with Blockrand 1.3 package using block randomization with randomly varying block size from 4 to 6 without stratification. The recruitment and allocation are done by the surgeon responsible for the decision to proceed to appendicectomy using a web-based service. After inputting inclusion and exclusion criteria the service will give the eligible patients' allocation group for both layers. The allocated intervention is open-label, and the patient, surgeon, other healthcare personnel, data collectors and data analysts are not blinded. The responsible surgeon will schedule an appendicectomy with allocated urgency[26] and either commences antibiotics or not based on the allocation.

Intervention

Preoperative treatment

Analgesia is given in accordance to normal clinical practice. All patients, regardless of their allocation group, will receive preoperative prophylactic antibiotics (intravenous cefuroxime 1500 mg and metronidazole 500 mg or a suitable alternative in case of allergy or other contraindication) within 30 minutes before the appendicectomy during induction of anaesthesia.

Preoperative antibiotic treatment

In the antibiotic group, the antibiotic treatment (cefuroxime 1500 mg and metronidazole 500 mg every 8 hours) is started immediately after the randomization and will continue until the induction of anaesthesia. Patients randomized to the no antibiotics group will receive preoperative antibiotics only at the induction of anaesthesia.

Surgery

All randomized patients are approached primarily laparoscopically unless there is a specific contraindication not to do so, and

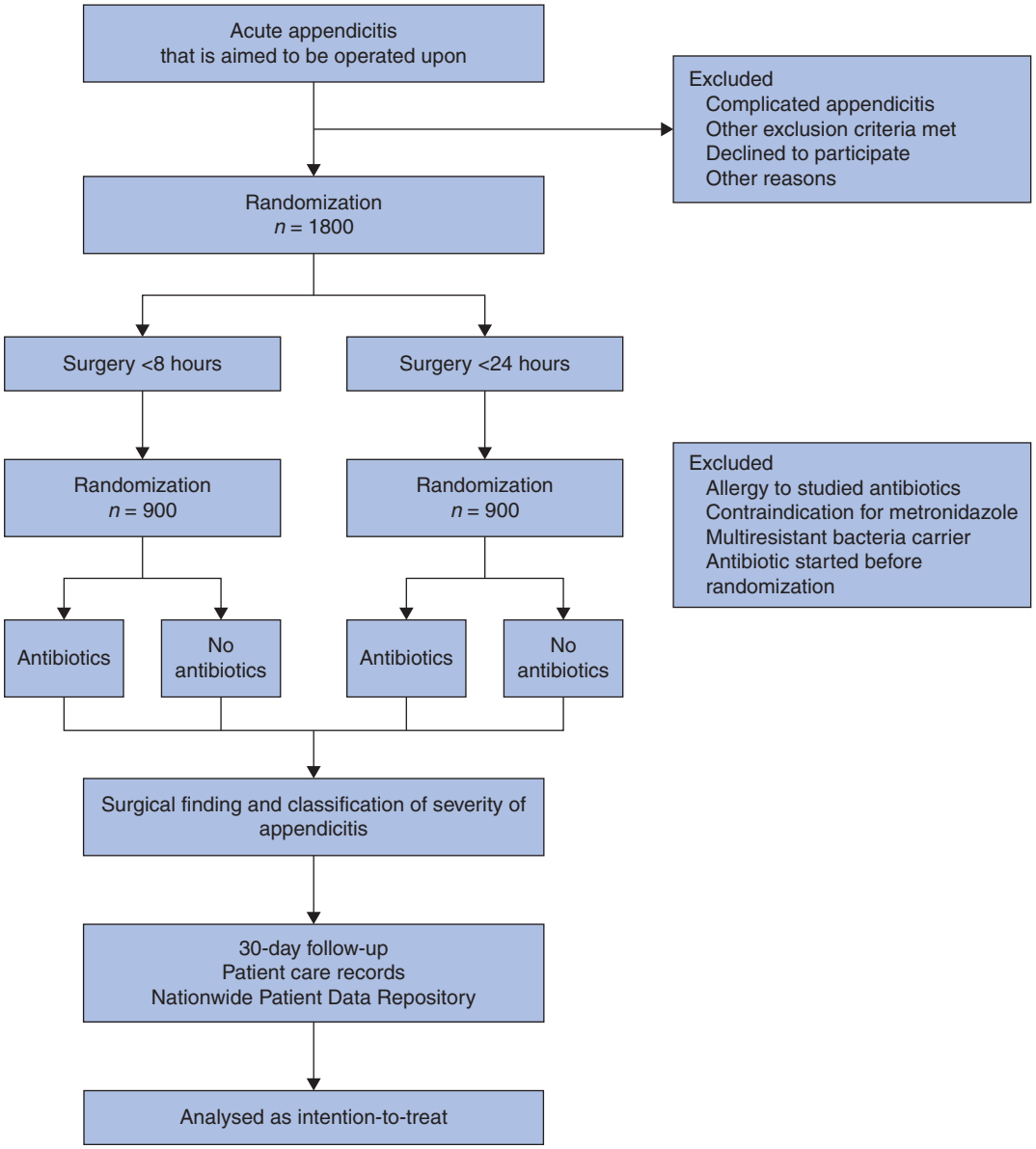

Fig. 1 Flow chart of patients in the trial

Table 1 American Association for the Surgery of Trauma grading scale for the severity of appendicitis

Grade	Operative criteria
0	Normal appendix
I	Acutely inflamed appendix, intact
II	Gangrenous appendix, intact
III	Perforated appendix with local contamination
IV	Perforated appendix with periappendiceal phlegmon or abscess
V	Perforated appendix with generalized peritonitis

laparoscopic surgery may be converted to open surgery at the decision of the operating surgeon. Appendicitis is classified intraoperatively according to American Association for the Surgery of Trauma (AAST) Grading Scale[27] (*Table 1*) and Sunshine Appendicitis Grading System (SAGS)[28] by the operating surgeon. The removed appendix is always sent for histopathological examination.

Postoperative treatment

Postoperative antibiotic treatment is similar in all study groups. When AAST grade is I–II, the appendicitis is regarded as uncomplicated and no further antibiotic treatment is needed. If the AAST grade is III–V, the appendicitis is categorized as complicated, and the antibiotic treatment will be continued at least 4 days postoperatively, of which at least 72 hours of treatment will be administered intravenously. The total duration of antibiotic treatment will be assigned at the discretion of the surgeon. Iatrogenic appendiceal perforation or other contamination during surgery does not change the aforementioned postoperative antibiotic policy.

Criteria for discharge

To allow discharge, there must be no further need for intravenous antibiotics, well controlled postoperative pain using normal analgesia (paracetamol, non-steroidal anti-inflammatory drug and/or weak opioid) and no fever (temperature less than 38.5°C).

Follow-up

No routine follow-up is scheduled. Patients are recommended to contact the hospital where the surgery was performed in case of any problems within 30 days after the surgery. Further, all patient visits and (re)admissions in Finland are recorded in the Nationwide Patient Data Repository (NPDR). The NPDR consists of all healthcare units' patient medical records from public or private medical clinics that are enrolled in Finland. All possible visits to a healthcare unit within 30 days of surgery will be checked and recorded from the NPDR.

Endpoints

The primary endpoint is complicated appendicitis AAST grade III–V[27] assessed by surgeon intraoperatively.

Secondary endpoints are duration of hospital stay after randomization (hours); complications within 30 days after surgery (Clavien–Dindo classification)[29]; preoperative pain assessed hourly by the patient using the numeric rating scale (NRS) whilst waiting for surgery (area under NRS curve); surgical-site infections within 30 days after randomization as defined by Centers for Disease Control (superficial, deep incisional, organ/space)[30]; positive blood culture within 30 days after randomization; rate of conversion to open surgery; histopathological diagnosis: gangrene or perforation; SAGS classification[28].

Data collection and analysis

Patients are requested to evaluate the pain they feel hourly whilst waiting for surgery by filling out the NRS form.

Data will be collected using an electronical case report form and from the patient care records. Interim analyses will be made when 300 and 900 patients have been randomized and operated on. Both layers (delay and antibiotics) undergo the same interim analyses. The Peto approach is used in planned interim analyses[31]. If there is a statistically significant difference in the main outcome with $P < 0.001$ (χ^2 test) between the study arms, the corresponding study layer is terminated. In the final analysis the difference of proportions of main outcome between the study arms with 95 per cent confidence intervals is calculated. Non-inferiority margin is set to 5 percentage points in both layers. Results from both study layers will be published as separate manuscripts in international peer-reviewed journals.

Sample size calculation

Twenty-two per cent of patients with uncomplicated appendicitis on CT were found to be perforated at operation in adults when median in-hospital waiting time for the surgery was over 8 hours[5]. In the same study, it was estimated that the risk of perforation increases by 2 per cent every hour. On the other hand, in patients with CRP less than 100 mg/l on admission, the rate of perforated appendicitis was 14 per cent[8].

The aim is to show that in patients with presumed uncomplicated appendicitis, scheduling appendicectomy within 24 hours does not lead to absolute increase in the rate of perforated appendicitis (AAST grade III–V) compared with scheduling the appendicectomy within 8 hours. It is assumed that in this patient population the rate of perforated appendicitis would be 15 per cent. The non-inferiority margin was set at 5 percentage points in difference of proportions of perforated appendicitis between the arms. To declare the non-inferiority, 1748 patients are needed to achieve a power of 90 per cent (χ^2) with 0.05 alpha. To take into account an assumed 2 to 3 per cent drop off rate, sample size is set to 1800 patients.

In the antibiotic layer, an identical (5 percentage points) non-inferiority margin in difference of proportions of perforated appendicitis was set with identical sample size calculation.

Patient recruiting started in May 2020 and the recruitment is estimated to take 2 years.

Ethics and permissions

Participation in this study is voluntary. All participants will give a written informed consent after they have had written information regarding the trial and a possibility to discuss the trial details. This study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The study has been approved by the Helsinki University Hospital ethics committee, Finnish Medicines Agency (Fimea), and the institutional review board of participating hospitals.

Discussion

Although there are numerous observational studies, both retrospective and prospective, regarding the delay to surgery in acute appendicitis with contradictory results, no prospective randomized controlled study has been published. As appendicectomy remains the standard for treatment of appendicitis with high efficiency and low complication rates[32] and since appendicitis is the most common emergency surgery, organizing urgent appendicectomies for vast numbers of patients remains a great burden for healthcare systems worldwide. Approximately 330 000, 75 000 and 6000 appendectomies take place in the USA, UK and Finland, respectively, every year[33]. Nearly one in 10 people will have appendicitis during their lifetime[34]. Consequently, the level of urgency of appendicectomy is of great importance. If it is safe to perform appendicectomy for presumed uncomplicated appendicitis within 24 hours, it will allow the surgery to be performed within office hours with enormous implications. For example, it allows treating these patients as day-case surgery, reduces costly and harmful night-time work and frees resources to other urgent emergency surgery.

On the other hand, it is of paramount importance to assess vigorously the safety of longer waiting for appendicectomy, since perforated appendicitis leads to higher morbidity rates[11] and longer hospital stay[10]. The selected primary endpoint, AAST grade III–V, is clinically relevant for patients and also for society because complications increase treatment costs. This study is the first to assess the role of appendicectomy delay in a prospective randomized study yielding level 1 evidence.

The second layer of the trial, antibiotic treatment before appendicectomy, is also of great importance. The increase of antimicrobial resistance is a major global threat, thus unnecessary antibiotic treatment should be avoided[35]. Prolonged antimicrobial treatment is associated with increased adverse effects, for example the occurrence of *Clostridium difficile* diarrhoea[36]. Excessive pharmacological treatment also increases the total medical costs. Antibiotic administration may not be a significant risk for an individual patient but treating large numbers of patients with increased overall use of antibiotics can affect the development of antibiotic resistance. However, if antibiotic treatment while waiting for appendicectomy reduces perforation rate, it could be worthwhile. There are several studies on the efficiency of preoperative antibiotic prophylaxis to prevent postoperative complications[19,21,37], but the impact on appendiceal perforation rate is not known.

In 2005, a large Cochrane meta-analysis agreed that broad-spectrum antibiotics given before surgery are effective in

decreasing postoperative wound infections and intra-abdominal abscesses, and the impact remains the same in single and multiple doses. No apparent difference in the nature of the removed appendix was determined[37]. Like the urgency layer, this trial is the first to assess the role of antibiotic treatment while waiting for appendicectomy in a prospective randomized trial.

In non-randomized studies, the delay to appendicectomy is affected by several variables, not least the decisions by the on-call surgeon. Most surgeons tend to operate on clinically sicker patients earlier, leading to longer delays in patients with milder symptoms, who at the same time have lower risk of perforation. This phenomenon leads to a possible false finding that the delay has no role or that it would be safe to delay the surgery. As such, this bias is very difficult to control in any other type of study than a randomized one. Further, many studies have not excluded the patients with a pre-hospital perforation and the in-hospital delay in these patients will not affect the perforation rate[6,7,11–13]. One study attempted to take this into account by excluding patients with presumed pre-hospital perforation from the analyses. In that study, the increment of in-hospital delay from less than 6 hours to more than 12 hours doubled the proportion of complicated appendicitis from 9.5 per cent to 18.9 per cent[8]. In this study the usage of antibiotics while waiting for the surgery was not uniform.

Preoperative distinction between uncomplicated and complicated forms of appendicitis is challenging[5,8,25,38]. There is no impeccable diagnostic method that would identify all complicated forms of acute appendicitis before surgery. This is the main limitation of this trial. If the trial used narrower inclusion criteria, complicated appendicitis could be excluded more accurately, but the results would not be generalized easily. The method to predict complicated appendicitis is pragmatic and easy to generalize because of its simplicity. The large number of patients needed is also a challenge. The recruitment takes place in the surgical emergency room often out of normal working hours.

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K.J. drafted the manuscript. All authors participated in the design of the trial and/or are the main organizing local investigators at the participating hospitals. All authors have read, revised and approved the final manuscript.

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