Role of preoperative in-hospital delay on appendiceal perforation while awaiting appendicectomy (PERFECT): a Nordic, pragmatic, open-label, multicentre, non-inferiority, randomised controlled trial

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Lancet 2023; 402: 1552–61

Published Online September 14, 2023 https://doi.org/10.1016/S0140-6736(23)01311-9

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Summary

Background Appendicectomy remains the standard treatment for appendicitis. No international consensus exists on the surgical urgency for acute uncomplicated appendicitis, and recommendations vary from surgery without delay to surgery within 24 h. Longer in-hospital delay has been thought to increase the risk of perforation and further morbidity. Therefore, we aimed to compare the rate of appendiceal perforation in patients undergoing appendicectomy scheduled to two different urgencies (<8 h *vs* <24 h).

Methods In this pragmatic, open-label, multicentre, non-inferiority, parallel, randomised controlled trial in two hospitals in Finland and one in Norway, patients (aged ≥18 years) with presumed uncomplicated acute appendicitis were randomly assigned (1:1) to an appendicectomy scheduled within 8 h or within 24 h to determine whether longer in-hospital delay (time between randomisation and surgical incision) is not inferior to shorter delay. Patients were excluded in cases of pregnancy, suspicion of perforated appendicitis (C-reactive protein level of ≥100 mg/L, fever >38·5°C, signs of complicated appendicitis on imaging studies, or clinical generalised peritonitis), or other reasons requiring prompt surgery. The recruiters were on-duty surgeons who decided to proceed with the appendicectomy. The randomisation sequence was generated using block randomisation with randomly varying block sizes and stratified by hospital districts; neither physicians nor patients were masked to group assignment. The primary outcome was perforated appendicitis diagnosed during surgery analysed in all patients who received an appendicectomy by intention to treat. The absolute difference in rates of perforated appendicitis was compared between the groups. Complications and other safety outcomes were analysed in all patients who received an appendicectomy. A margin of 5 percentage points was used to establish non-inferiority. This trial was registered at ClinicalTrials.gov (NCT04378868) and is closed to accrual.

Findings Between May 18, 2020, and Dec 31, 2022, 2095 patients were assessed for eligibility, of whom 1822 were randomly assigned to appendicectomy scheduled within 8 h (n=914) or 24 h (n=908). After randomisation, 19 (1%) of 1822 patients were excluded due to protocol violation. 1803 patients were included in the intention-to-treat analyses, 985 (55%) of whom were male and 818 (45%) female. Appendiceal perforation rate was similar between groups (77 [8%] of 907 patients assigned to the <8 h group and 81 [9%] of 896 patients assigned to the <24 h group; absolute risk difference 0·6% [95% CI −2·1 to 3·2], p=0·68; risk ratio 1·065, 95% CI 0·790 to 1·435). No significant difference was found between the complication rates within 30 days (66 [7%] of 907 patients in the <8 h group *vs* 56 [6%] of 896 patients in the <24 h group; difference −1·0% [−3·3 to 1·3]; p=0·39), and no deaths occurred during this follow-up period.

Interpretation In patients with presumed uncomplicated acute appendicitis, scheduling appendicectomy within 24 h does not increase the risk of appendiceal perforation compared with scheduling appendicectomy within 8 h. The results can be used to allocate operating room resources, for example postponing night-time appendicectomy to daytime.

Funding The Finnish Medical Foundation, Mary and Georg Ehrnrooth's Foundation, Biomedicum Helsinki Foundation, and the Finnish Government.

Introduction

The surgical urgency of acute appendicitis has been debated for decades since appendicectomy is one of the most frequently performed emergency surgeries.[1] Evidence suggests that a longer waiting time for surgery from symptom onset increases the risk of complicated appendicitis.[2–4] However, the effect of in-hospital delay has been inconclusive.[2,3,5–10] Guidelines recommend performing appendicectomy without delay[11,12] or within 24 h while minimising the delay

Research in context

Evidence before this study

The perception that appendicitis rapidly progresses into perforation has resulted in performing appendicectomy without delay. Prolonged symptom duration is associated with complicated appendicitis; however, studies on in-hospital delays have produced conflicting results, and international guideline recommendations vary. We searched PubMed with the search terms "appendicitis (all fields)", and "delay (title/abstract)", for publications published in English from database inception to Sept 4, 2019. Two large retrospective meta-analyses between 2014 and 2018 suggested that a delay of less than 24 h does not increase the risk of complicated appendicitis or postoperative complications in patients with presumed uncomplicated appendicitis. However, no randomised studies were found, and meta-analyses were based on observational cohort studies, which naturally include a selection bias.

Added value of this study

To our knowledge, this is the first study to assess the role of appendicectomy delay in a prospective randomised trial. This study was a large trial that included 1803 patients with presumed uncomplicated appendicitis. We found that scheduling appendicectomy within 24 h in patients with presumed uncomplicated acute appendicitis did not increase the appendiceal perforation rate, severity of appendiceal inflammation, spread of purulent discharge, presence of periappendicular abscesses, or postoperative complications compared with those scheduled for appendicectomy within 8 h.

Implications of all the available evidence

Appendectomies do not need to be performed emergently as delay does not increase the risk of complications in uncomplicated acute appendicitis. This finding might facilitate the scheduling of appendectomies. For example, postponing surgery from night-time to daytime can free up resources for other emergency surgeries.

wherever possible[13] on the basis of retrospective reports suggesting that preoperative in-hospital delay increases the risk of appendiceal perforation.[2,7,8,14] Conversely, two large meta-analyses based on retrospective studies estimated that postponing surgery for up to 24 h is safe for patients without preoperative signs of complicated appendicitis.[5,10] However, all retrospective studies are biased because patients with more severe symptoms are usually treated faster, favouring longer waiting times for patients with milder symptoms. Appendicectomy is the standard treatment for acute appendicitis,[11–13] although spontaneous resolution with or without antibiotics has also been shown.[15–17] Additionally, daily clinical practice varies substantially because of contradictory results based on in-hospital delay. Some hospitals schedule night-time appendectomies whereas others are done during the day.[6,18]

Patients with acute uncomplicated appendicitis tolerate laparoscopic appendicectomy well and recovery is usually straightforward with minimal risk of complications.[11,13] Nevertheless, surgery becomes more complex, and morbidity, hospitalisation, costs, and use of broad-spectrum antibiotics increase if the inflammation progresses to perforation (ie, complicated appendicitis).[7,18–20] Therefore, establishing the appropriate time to perform an appendicectomy is particularly important. To our knowledge, no randomised controlled trials assessing different urgency levels for appendectomies have been done.

We conducted a randomised controlled trial to compare the rate of appendiceal perforation in patients with predicted uncomplicated appendicitis scheduled for surgery of two different urgencies.[21] Our hypothesis was that a longer in-hospital delay from randomisation to surgical incision is not inferior to a shorter delay; therefore, we used a non-inferiority trial setting.

Methods

Study design

The PERFECT trial was a pragmatic, open-label, multicentre, non-inferiority, parallel, randomised controlled trial comparing appendectomies scheduled within 8 h and 24 h in adult patients with predicted uncomplicated acute appendicitis. The trial was performed in two hospitals in Finland (Meilahti Tower Hospital, Helsinki, and Jorvi Hospital, Espoo) and one in Norway (Akershus University Hospital, Oslo). All participating hospitals are academic teaching hospitals, serving as a secondary and tertiary centre for surgical patients.

The study was conducted in accordance with the protocol, which was published in September, 2021.[21] The protocol remained unchanged after commencing the trial, except for the addition of a new hospital. The trial included another round of randomisation, which assessed the use of preoperative antibiotics while patients awaited the operation: these results will be reported separately.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The ethics committees and Institutional Review Boards of Helsinki University Hospital and Akershus University Hospital provided ethics approval. The study was reported in concordance with the CONSORT statement.[22]

Participants

Eligible patients were adults (aged ≥18 years) diagnosed with acute appendicitis and scheduled for urgent appendicectomy. Acute appendicitis was diagnosed either clinically using the Adult Appendicitis Score (≥16)[23] or using radiological imaging with ultrasonography, CT, or MRI. Before randomisation, diagnostic imaging was recommended for all patients with symptoms occurring for more than 3 days[4] to rule out complicated forms of appendicitis. Exclusion criteria included no written consent, pregnancy, or suspicion of complicated (ie, perforated) appendicitis (eg, C-reactive protein concentration ≥100 mg/L,[8] body temperature >38·5°C, signs of complicated appendicitis on imaging studies, or clinical generalised peritonitis), or other reasons requiring prompt surgery. A list of radiological findings suggestive of complicated appendicitis was included in the protocol.[21] Sex data were collected from medical records based on the patient's social identification number. All participants provided written informed consent.

Randomisation and masking

The hospitals used a traffic light coding system for emergency surgical operations. Red codes indicated surgery within 8 h and orange codes within 24 h.[24] Eligible patients were randomly assigned (1:1) to appendectomies scheduled within 8 h (red group) or 24 h (orange group) using block randomisation (R, Blockrand 1.3) with varying block sizes of 4–6. Randomisation was stratified by hospital districts and concealed from the recruiters, treating physicians, surgeons, and researchers.

The recruiters included on-duty surgeons and surgical residents who decided whether participants should proceed with the appendicectomy. After inputting inclusion and exclusion criteria, a web-based service provided the patient allocation group, and the responsible surgeon scheduled an appendicectomy with an allocated urgency.[24] Patients, care providers, outcome assessors, and data analysts were not masked to group assignment. Patients were simultaneously randomly assigned 1:1 in a similar way to receive antibiotics or not while awaiting surgery if they had no exclusion criteria.

Procedures

Participants were scheduled for appendicectomy within 8 h or within 24 h and remained in hospital to await surgery. Preoperative delay was defined as the time between randomisation and surgical incision. The times of randomisation and surgical incision were recorded as they happened. Patients were requested to evaluate their pain hourly using a numerical rating scale form while waiting for surgery (0 indicated no pain and 10 indicated severe pain). If needed, the patients received pain medication after the standard clinical practice.

Patients were also allocated to wait for surgery without antibiotics or with antibiotics (primarily cefuroxime 1500 mg and metronidazole 500 mg intravenously every 8 h) during the waiting period, provided they had no contraindications. The surgical approach was primarily laparoscopic unless there was a specific reason to proceed directly to open appendicectomy. The operating surgeon classified appendicitis intraoperatively according to the American Association for the Surgery of Trauma (AAST) grading scale[25] and the Sunshine Appendicitis Grading Scale (SAGS).[26] The AAST grading scale assigns a score of 0 for no appendicitis and has five severity grades (1–5) of appendicitis; grade 1 represented mild non-gangrenous appendicitis and grades 3–5 represented perforated appendicitis. SAGS assigns a score of 0 for no appendicitis and has four severity grades (1–4); grade 4 indicated perforated appendicitis whereas 1–3 indicated non-perforated appendicitis. The excised appendix was sent for histopathological examination by pathologists.

According to the local hospital protocol, postoperative care, laboratory tests, blood cultures, and imaging studies were performed on clinical indications. The prespecified criteria for discharge were no longer requiring intravenous antibiotics, postoperative pain controlled with oral analgesia, and no fever. Patients were instructed to contact the hospital where the surgery was performed within 30 days in case of any concerns.

Outcomes

The primary endpoint was complicated appendicitis (ie, perforated appendicitis, defined as AAST grades 3–5[25]) assessed by the surgeon intraoperatively. Secondary prespecified endpoints included duration of hospital stay after randomisation; surgical site infections within 30 days after randomisation as defined by the US Centers for Disease Control and Prevention;[27] positive blood cultures (ie, microbiological growth in the blood) within 30 days after randomisation; all post-operative complications within 30 days (Clavien–Dindo classification 1–5);[28] patient-reported pain using the numerical rating scale while waiting for surgery (area under the numerical rating scale curve); rate of conversion to open surgery; histopathological diagnosis of gangrene versus perforation; and SAGS classification.[26] Post-hoc outcomes included risk of perforation in patients with appendicolith and the time distribution of perforations within urgency groups.

All complications occurring within 30 days of surgery were reviewed and reported from the local and nationwide electronic patient registers (detailed information on the Finnish Nationwide Patient Data Repository can be found in the protocol).[21] Data were collected using an electronic case report form in Finland and the RedCap web application in Norway. If a patient had two different complications, only the worst was reported. All collected variables and outcomes are defined in the appendix (p 2).

The prespecified interim safety analyses were performed when 300 patients and 900 patients were randomly assigned and had an appendicectomy. Since

neither interim analysis showed a significant difference (p<0·001) in the perforation rate between the groups, the trial was completed as planned.

Statistical analysis

Based on previously published studies[8,14] from the Helsinki University Hospital, we estimated that 15% of patients who met the inclusion criteria would be diagnosed with complicated appendicitis perioperatively. A margin of 5 percentage points was calculated to assess non-inferiority in the difference in the proportion of perforated appendicitis between the groups. We calculated that 1800 patients were needed (considering a dropout rate of approximately 3%) to achieve a power of 90% (χ^2) with an α value of 0·05 (one-sided 95% CI).[21]

The primary and secondary endpoints were analysed in all patients who were randomly assigned and received an appendicectomy, according to intention to treat. Effect sizes were reported as absolute differences between proportions for categorical variables, with two-sided 95% CIs calculated using the traditional Wald method or Cramér's V for categorical multivariables. The risk ratio (RR) with 95% CI was also calculated to compare perforation rate between patients scheduled for appendicectomy within 8 h or within 24 h. p values were calculated for categorical variables using Pearson's χ^2 or Fisher's exact test (if the sample size in one cell was fewer than five) and normally distributed continuous variables using an independent samples *t* test. A two-tailed p<0·05 was considered significant. For the non-normally distributed continuous variables, natural logarithms were taken to obtain normally distributed data, and an independent samples *t* test was used for between-group comparisons. The geometric mean was calculated using the anti-log function, and the effect size was reported as the ratio of geometric means with 95% CI. The Mann-Whitney *U* test was used if a log transformation could not be performed. In this case, the effect size was reported as *r*, which was calculated as $Z/\sqrt{N}$ without a 95% CI. However, in post-hoc explanatory analyses in patients with CT-diagnosed appendicolith, the RR with 95% CI was calculated to compare the perforation rate between patients with and without appendicolith. The evidence for non-inferiority of the primary outcome was quantified using Bayes factor for non-inferiority design as described by van Ravenzwaaij and colleagues.[29] Additionally, we did a post-hoc explanatory analysis to compare the perforation rate between patients with and without appendicolith. For primary and secondary outcomes, we did a post-hoc subgroup analysis in patients assessed per protocol (ie, operated on within 8 h or within 24 h) and a modified per-protocol analysis (ie, in patients operated on within 8 h and at 8–24 h). Furthermore, we did a post-hoc analysis regarding the waiting time among patients with perforation in both groups. Patients who did not return numerical rating scale forms or provided incomplete forms were excluded from pain analyses.

All statistical analyses were performed using SPSS (version 25). There was no designated data monitoring committee for this trial. The trial was registered at ClinicalTrials.gov (NCT04378868) and is closed to accrual.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 18, 2020, and Dec 31, 2022, 2095 patients were recruited in Finnish research hospitals and a Norwegian hospital and assessed for eligibility.

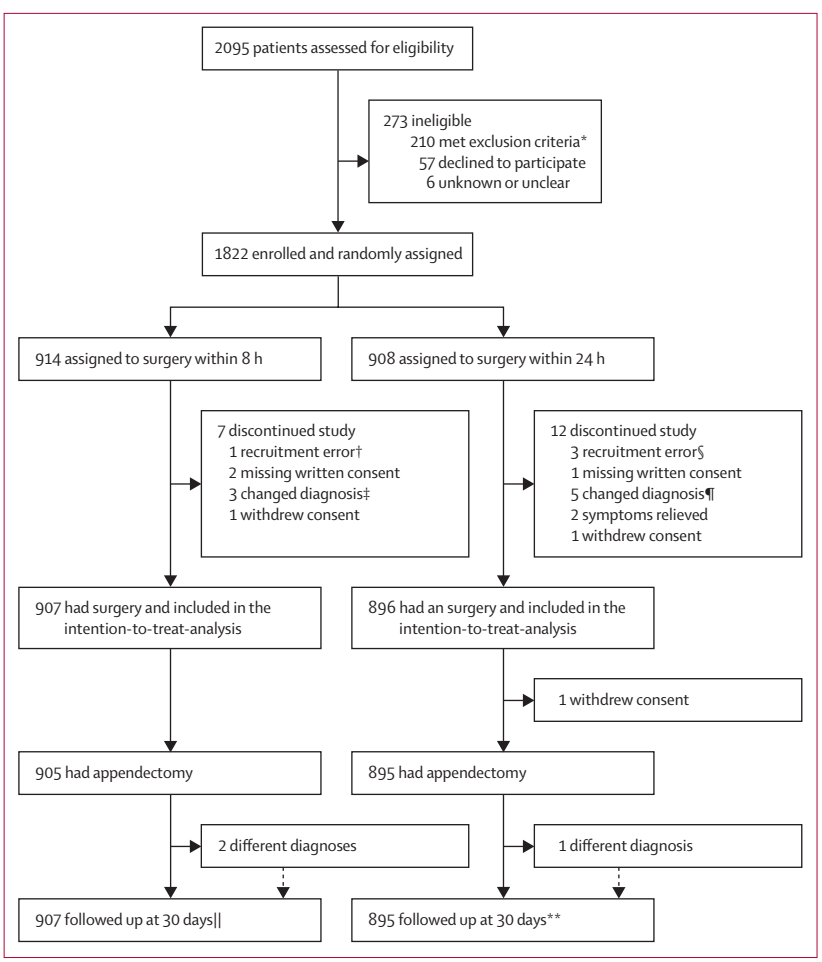

***Figure*: Trial profile**

NPDR=Nationwide Patient Data Repository. *Patients might have more than one exclusion criterion. Criteria were aged younger than 18 years (n=24), C-reactive protein level of 100 mg/L or more (n=117), fever more than 38·5°C (n=38), complicated appendicitis on imaging (n=84), pregnancy (n=6), and requring urgent operation due to generalised peritonitis or other (n=31). †Patient had anaesthesiology contraindication for urgent surgery. ‡Changed diagnoses were lymphadenitis (n=1), gynaecological diagnosis (n=1), and diabetic ketoacidosis (n=1). §Recruitment errors were a fever higher than 38·5°C (n=1), CT-verified perforation before randomisation (n=1), and suspicion of peritonitis (n=1). These three patients met exclusion criteria before randomisation and were mistakenly allocated due to human error. ¶Changed diagnoses were colon diverticulitis (n=1), duodenum diverticulitis (n=1), bacterial enteritis (n=2), and gynaecological diagnosis (n=1). ||829 patients were also followed up from the Finnish NPDR. **810 patients were also followed up from the Finnish NPDR.

	Red group, <8 h (n=907)	Orange group, <24 h (n=896)
Sex		
Male	514 (57%)	471 (53%)
Female	393 (43%)	425 (47%)
Age, years	35 (28–46)	35 (28–47)
ASA score		
1	481 (53%)	463 (52%)
2	368 (41%)	353 (39%)
3	58 (6%)	78 (9%)
4	0	2 (<1%)
CACI	0	0 (0–1)
CACI ≥2	104 (12%)	121 (14%)
BMI	25·7 (23·1–29·3)	26·0 (23·4–29·4)
Missing	97 (11%)	95 (11%)
Asthma	44 (5%)	43 (5%)
Hypertension	82 (9%)	94 (10%)
Immunosuppressive medication	26 (3%)	30 (3%)
C-reactive protein, mg/L	24 (6–49)	25 (8–50)
White blood cell count, $\times 10^9$ per L	12·3 (4·0)	12·4 (3·8)
Fever, °C	37·1 (0·5)	37·1 (0·6)
Adult Appendicitis Score	14 (3)	14 (3)
Imaging verified	742 (82%)	779 (87%)
CT	605 (67%)	619 (69%)
Appendicolith on CT*	209 (35%)	202 (33%)
Ultrasound	135 (15%)	159 (18%)
MRI	2 (<1%)	1 (<1%)
Appendix thickness,† mm	11 (9–12)	11 (9–13)
Received antibiotics while waiting for surgery	466 (51%)	432 (48%)
Duration of symptoms before randomisation, h	24 (15–35)	24 (16–36)
1–12	120 (13%)	140 (16%)
>12 and ≤24	359 (40%)	326 (36%)
>24 and ≤36	213 (24%)	207 (23%)
>36 and ≤48	89 (10%)	101 (11%)
>48 and ≤72	70 (8%)	71 (8%)
>72	56 (6%)	50 (6%)
Missing	0	1 (<1%)

Data are n (%), median (IQR), or mean (SD). Due to rounding, percentages might not total 100. ASA=American Society of Anesthesiology. CACI=Charlson age comorbidity index. *Percentages are calculated from patients imaged with CT. †Measured from the images.

Table 1: **Baseline characteristics and clinical findings on admission**

1822 patients were enrolled and randomly assigned to appendicectomy within 8 h (914 in the red group) or within 24 h (908 in the orange group; figure). After randomisation, 19 (1%) of 1822 patients were excluded. 1803 patients had surgery (907 in the red group, and 896 in the orange group); two patients in the red group and one in the orange group did not have appendicectomy because a different diagnosis was found intraoperatively. Additionally, one patient withdrew consent in the orange group. However, all 1803 participants were included in the intention-to-treat analysis. Baseline characteristics were similar between groups (table 1). The median duration of symptoms before randomisation was 24 h in both groups. Surgery was performed within 8 h in 574 (63%) of 907 patients in the red group and within 24 h in 792 (88%) of 896 patients in the orange group. The median preoperative delay from randomisation to incision was 6 h (IQR 3–10) in the red group and 14 h (IQR 8–20) in the orange group (difference 8 h; table 2). Similarly, the length of hospital stay was 8 h shorter in the red group than in the orange group (table 2). Of 896 patients in the orange group, 214 (24%) underwent appendicectomy within 8 h. Approximately half of the patients in both groups received antibiotics while waiting for appendicectomy (table 1).

Perforated appendix occurred in 158 (9%) of 1803 patients: 77 (8%) of 907 patients in the red group and 81 (9%) of 896 patients in the orange group (absolute difference 0·6% [95% CI –2·1 to 3·2], p=0·68; RR 1·065, 95% CI 0·790–1·435; table 2). Since the non-inferiority margin was set at 5 percentage points, this result met the non-inferiority criteria. For the primary endpoint, Bayes factor was 1764·01, which indicates that the non-inferiority hypothesis is 1764 times more likely than the inferiority hypothesis, given the data.

The distribution of the different AAST and SAGS grades were similar, and histological diagnoses were similar between the groups (table 2).

All operations started laparoscopically, and the operation time from incision to skin closure was similar between the groups at approximately 45 min (table 2). The conversion rates (all due to surgical technical challenges) were low (<1%) and did not differ between the groups (table 2).

No difference in the overall complication rate within 30 days (any Clavien–Dindo grade) was found between the groups (table 2). Because one patient in the orange group withdrew consent, only 1802 patients were available for 30 day follow-up; postoperative complications occurred in 122 (7%) patients. However, overall, only 19 (1%) of 1802 patients required intervention (table 2). Additionally, two different complications occurred in ten patients, one of whom underwent reoperation twice (four [<1%] of 907 in the red group and six [1%] of 895 in the orange group). The rate of surgical site infection and distribution of incisional and intra-abdominal surgical site infections were similar in both groups (table 2). Six (1%) of 907 patients in the red group and eight (1%) of 895 patients in the orange group required percutaneous drainage or reoperation due to surgical site infection. The frequency of positive blood cultures after randomisation was similar between the groups (table 2). A detailed list of complications is provided in the appendix (p 3).

The average hourly pain between randomisation and surgery was similar between groups. However, as the

	Red group, <8 h (n=907)	Orange group, <24 h (n=896)	p value	Effect size (95% CI)
Primary outcomes				
Perforated appendicitis (AAST 3–5)	77 (8%)	81 (9%)	0·68*	Difference 0·6% (–2·1 to 3·2)
AAST 0—normal appendix	23 (3%)	16 (2%)	NA	NA
AAST 1—acutely inflamed appendix, intact	682 (75%)	689 (77%)	NA	NA
AAST 2—gangrenous appendix, intact	125 (14%)	110 (12%)	NA	NA
AAST 3—perforated, local contamination	39 (4%)	29 (3%)	NA	NA
AAST 4—perforated with peri-appendiceal phlegmon or abscess	23 (3%)	29 (3%)	NA	NA
AAST 5—perforated with generalised peritonitis	15 (2%)	23 (3%)	NA	NA
Secondary outcomes				
Geometric mean duration of hospital stay, h	31 (1·7)	39 (1·6)	<0·0001†	Geometric mean ratio 0·8 (0·7 to 0·8)
Laparoscopic procedure	902 (99%)	892 (<100%)	1·0‡	Difference 0·1% (–0·5 to 0·8)
Conversion	5 (1%)	4 (<1%)	1·0‡	Difference –0·1% (–0·8 to 0·5)
SAGS	NA	NA	0·70*	0·03§
0—no appendicitis	23 (3%)	16 (2%)	NA	NA
1—simple appendicitis	667 (74%)	665 (74%)	NA	NA
2 and 3—purulent discharge locally or in four quadrants¶	140 (15%)	134 (15%)	NA	NA
Pathological verification‖	NA	NA	0·28*	0·04§
Non-perforated gangrenous appendix	79 (9%)	60 (7%)	NA	Difference –2·0% (–4·5 to 0·4)
Perforated appendix	80 (9%)	81 (9%)	NA	Difference 0·2% (–2·4 to 2·9)
30 day follow-up**				
Complication rate ≤30 days	66 (7%)	56 (6%)	0·39*	Difference –1·0% (–3·3 to 1·3)
Clavien–Dindo grade 1	14 (2%)	12 (1%)	NA	NA
Clavien–Dindo grade 2	43 (5%)	34 (4%)	NA	NA
Clavien–Dindo grade 3a + b and 4a	9 (1%)	10 (1%)	NA	NA
Surgical site infection	24 (3%)	22 (2%)	0·80*	Difference –0·2% (–1·6 to 1·3)
Superficial and deep incisional infection	11 (1%)	10 (1%)	NA	NA
Intra-abdominal infection	13 (1%)	12 (1%)	NA	NA
Positive blood culture	4 (<1%)	6 (1%)	0·55‡	Difference 0·2% (–0·5 to 0·9)
NRS for pain				
NRS average value per h	4·0 (2·3)	3·9 (2·2)	0·46††	Difference 0·2 (–0·2 to 0·5)
Area under NRS curve	18 (9–36)	45 (19–76)	<0·0001‡‡	–0·4§§
Incompletely filled or unreturned NRS forms	610 (67%)	610 (68%)	NA	NA
Other details				
Preoperative delay, h¶¶	6 (3–10)	14 (8–20)	NA	NA
Operating time, min	44 (34–61)	44 (33–59)	NA	NA
Histopathological examination				
No appendicitis	24 (3%)	17 (2%)	NA	NA
Simple appendicitis	768 (85%)	782 (87%)	NA	NA
Gangrenous appendix	104 (11%)	89 (10%)	NA	NA
Chronic appendicitis	6 (1%)	2 (<1%)	NA	NA
Other findings	2 (<1%)	2 (<1%)	NA	NA
Missing	3 (<1%)	4 (<1%)	NA	NA
Malignant or premalignant tumour	21 (2%)	18 (2%)	NA	NA
Other diagnoses‖‖	17 (2%)***	11 (1%)†††	NA	NA

Data are n (%), median (IQR), mean (SD), or geometric mean (SD). Due to rounding, the percentage differences might differ from the data presented, and percentages might not total 100. AAST=American Association for the Surgery of Trauma grading scale. SAGS=Sunshine Appendicitis Grading Scale. NA=not applicable. NPDR=Nationwide Patient Data Repository. NRS=numerical rating scale. *Pearson's χ^2 test. †Independent samples *t* test after logarithmic transformation. ‡Two-sided Fisher's exact test. §Cramér's V. ¶SAGS 3, purulent discharge in four quadrants, was detected, one in the red group and four in the orange group. ‖Includes macroscopic and microscopic perforations (histopathological examination revealed three microscopic perforations in the red group and none in the orange group that had not been detected clinically). **One patient in the orange group withdrew consent and is excluded from the 30 day follow-up. The 30 day follow-up of 163 patients could only be done from the hospitals' internal database without the NPDR search. One patient went to another hospital district for treatment due to fever; however, we do not have additional information regarding this complication. Clavien–Dindo 4a was observed in one patient in the orange group and none in the red group. If a patient had two different complications, only the worst was reported. Surgical site infections were deep incisional (one in the orange group and none in the red group). ††Independent samples *t* test. ‡‡Mann-Whitney *U* test. §§r=Z/√N without 95% CI. ¶¶Preoperative delay is the time between randomisation and surgical incision with missing data for one patient in the red group and none in the orange group. ‖‖For patients with a clinically intact appendix, the appendix was clinically normal but histologically infected in six patients in the red group and five patients in the orange group. ***Other intestinal diagnoses (n=7), lymphadenitis (n=2), gynaecological diagnosis (n=3), urinary tract infection (n=1), and non-specific abdominal pain (n=4). †††Gynaecological diagnosis (n=3), diverticulitis (n=1), ureterolithiasis (n=1), and non-specific abdominal pain (n=6).

Table 2: **Outcomes in the intention-to-treat population**

	Red group, <8 h (n=574)	Orange group, 8–24 h (n=578)	p value	Effect size (95% CI)
Primary outcomes				
Perforated appendicitis (AAST 3–5)	43 (7%)	61 (11%)	0·070*	Difference 3·1% (–0·2 to 6·4)
AAST 0—normal appendix	12 (2%)	12 (2%)	NA	NA
AAST 1—acutely inflamed appendix, intact	445 (78%)	429 (74%)	NA	NA
AAST 2—gangrenous appendix, intact	74 (13%)	76 (13%)	NA	NA
AAST 3—perforated, local contamination	23 (4%)	21 (4%)	NA	NA
AAST 4—perforated with peri-appendiceal phlegmon or abscess	12 (2%)	23 (4%)	NA	NA
AAST 5—perforated with generalised peritonitis	8 (1%)	17 (3%)	NA	NA
Secondary outcomes				
Geometric mean duration of hospital stay, h	27 (1·7)	44 (1·0)	<0·0001†	Geometric mean ratio 0·6 (0·58 to 0·65)
Laparoscopic procedure	570 (99%)	576 (<100%)	0·45‡	Difference 0·3% (–0·5 to 1·2)
Conversion	4 (1%)	2 (<1%)	0·45‡	Difference –0·4% (–1·2 to 0·5)
SAGS	NA	NA	0·34*	0·3§
0—no appendicitis	12 (2%)	12 (2%)	NA	NA
1—simple appendicitis	433 (75%)	418 (72%)	NA	NA
2 and 3—purulent discharge locally or in four quadrants¶	86 (15%)	87 (15%)	NA	NA
Pathological verification‖	NA	NA	0·19*	0·03§
Non-perforated gangrenous appendix	44 (8%)	43 (7%)	NA	Difference –0·2% (–3·3 to 2·8)
Perforated appendix	43 (7%)	61 (11%)	NA	Difference 3·1% (–0·2 to 6·4)
30 day follow-up**				
Complication rate ≤30 days	43 (7%)	34 (6%)	0·23*	Difference –1·6% (–4·5 to 1·3)
Clavien–Dindo grade 1	8 (1%)	5 (1%)	NA	NA
Clavien–Dindo grade 2	28 (5%)	20 (3%)	NA	NA
Clavien–Dindo grade 3a + b and 4a	7 (1%)	9 (2%)	NA	NA
Surgical site infection	17 (3%)	14 (2%)	0·57*	Difference –0·5% (–2·4 to 1·3)
Superficial and deep incisional infection	6 (1%)	4 (1%)	NA	NA
Intra-abdominal infection	11 (2%)	10 (2%)	NA	NA
Positive blood culture	2 (<1%)	6 (1%)	0·29‡	Difference 0·7% (–0·3 to 1·6)
NRS for pain				
NRS average value per h	4·0 (2·3)	3·8 (2·1)	0·45††	Difference 0·2 (–0·3 to 0·6)
Area under NRS curve	13 (7–24)	55 (32–82)	<0·0001‡‡	–0·6§§
Incompletely filled or unreturned NRS forms	375 (65%)	382 (66%)	NA	NA
Other details				
Preoperative delay, h	4 (2–6)	15 (12–20)	NA	NA
Operating time, min	42 (34–60)	46 (35–60)	NA	NA
Histopathological examination				
No appendicitis	12 (2%)	13 (2%)	NA	NA
Simple appendicitis	498 (87%)	497 (86%)	NA	NA
Gangrenous appendix	55 (10%)	63 (11%)	NA	NA
Chronic appendicitis	4 (1%)	1 (<1%)	NA	NA
Other findings	2 (<1%)	1 (<1%)	NA	NA
Missing	3 (1%)	3 (0·5%)	NA	NA
Malignant or premalignant tumour	14 (2%)	10 (2%)	NA	NA
Other diagnoses¶¶	8 (1%)‖‖‖‖	8 (1%)***	NA	NA

Data are n (%), median (IQR), mean (SD), or geometric mean (SD). Due to rounding, the percentage differences might differ from the data presented, and percentages might not total 100. AAST=American Association for Surgery of Trauma grading scale. NA=not applicable. NRS=numerical rating scale. SAGS=Sunshine Appendicitis Grading Scale. *Pearson's χ^2 test. †Independent samples *t* test after logarithmic transformation. ‡Two-sided Fisher's exact test. §Cramér's V. ¶SAGS 3, purulent discharge in four quadrants, was detected, one in the red group and four in the orange group. ‖Includes macroscopic and microscopic perforations (no microscopic perforations detected in either group).**Clavien–Dindo 4a was observed in one patient in the orange group and none in the red group. If a patient had two different complications, only the worst is reported. Surgical site infections were deep incisional (one in the orange group and none in the red group). Preoperative delay is the time between randomisation and surgical incision with missing data (one patient in the red group and none in the orange group). ††Independent samples *t* test. ‡‡Mann-Whitney *U* test. §§r=Z/√N without 95% CI. ¶¶In patients with clinically intact appendix, the appendix was clinically normal but histologically infected in four patients in both groups. ‖‖‖Other intestinal diagnoses (n=5), gynaecological diagnosis (n=1), and non-specific abdominal pain (n=2). ***Gynaecological diagnosis (n=3), diverticulitis (n=1), ureterolithiasis (n=1), and non-specific abdominal pain (n=3).

Table 3: **Outcomes in the modified per-protocol population**

waiting time increased, the area under the numeric rating scale curve also increased in the orange group (table 2).

Histologically verified negative appendectomies were performed in 24 (3%) of 907 patients in the red group and 17 (2%) of 896 patients in the orange group. In one patient with a clinically gangrenous appendix, the histopathological diagnosis was confirmed as a low-grade appendiceal mucinous neoplasm without acute infection. However, appendiceal neoplasia was observed in 21 (2%) of 907 patients in the red group and 18 (2%) of 896 in the orange group. Ten tumours were malignant, seven in the red group and three in the orange group (appendix p 4).

A post-hoc subgroup analysis from patients with appendiceal appendicolith detected on preoperative CT (table 1) did not show a significant difference in perforation rate between the groups (31 [15%] of 209 patients in the red group and 38 [19%] of 202 patients in the orange group; absolute difference 4·0%, 95% CI –3·3 to 11·2; p=0·28). However, patients with an appendicolith detected in the preoperative CT scan had an overall higher risk of perforation (69 [17%] of 411 patients with appendicoliths and 39 (5%) of 813 patients without; RR 3·500, 95% CI 2·407 to 5·088; p<0·0001).

Because a proportion of participants waited for surgery longer than intended, a post-hoc per-protocol analysis was performed to further substantiate the results of the intention-to-treat analyses. Per-protocol analyses included only patients who were operated on within the scheduled time (<8 h in 574 [63%] of 907 patients in the red group and <24 h in 792 [88%] of 896 patients in the orange group). The results of the per-protocol analyses were similar to those of the intention-to-treat analyses (appendix pp 6–7). Additionally, because 214 (24%) of 896 patients in the orange group were operated on in less than 8 h, we performed an additional post-hoc modified per-protocol analysis of patients operated on within 8 h in the red group and 8–24 h in the orange group (table 3; appendix p 8). These analyses show a small but insignificant increase in perforation rate in patients operated on in 8–24 h (absolute difference 3·1%, 95% CI –0·2 to 6·4; p=0·070). Furthermore, we did a post-hoc analysis of the actual waiting time in both groups separately. The median waiting time in the orange group was slightly longer for patients with perforation than for patients without perforation (17 h, IQR 11–23 *vs* 14 h, IQR 8–20; p=0·0039). Such difference was not found in the red group (6 h, 3–14 *vs* 6 h, 3–10; p=0·10).

Discussion

This pragmatic, multicentre, randomised controlled trial on surgical urgency for presumed uncomplicated appendicitis found that scheduling appendicectomy within 24 h was non-inferior to scheduling appendicectomy within 8 h. No increase was observed in the inflammation severity spread of purulent discharge into the abdominal cavity or peri-appendicular abscesses because of the prolonged waiting time. Additionally, no differences were observed in the rates of postoperative complications or surgical site infections. The benefits of a shorter delay to surgery were shorter duration of discomfort during the waiting time and length of hospital stay.

To the best of our knowledge, this is the first published randomised controlled trial on preoperative in-hospital delays for acute appendicitis. This trial provides the best evidence to date regarding the urgency of appendicectomy in this patient population. In previous non-randomised studies, perforation during appendicectomy was observed in 16–22% of patients who were thought to have non-perforated appendicitis before surgery.[14,15] In this study, the overall perforation rate was lower than these previous studies (158 [9%] of 1803 patients), suggesting that the inclusion and exclusion criteria were well designed to reduce the risk of complicated appendicitis. Our study is consistent with previous publications[6,8] because it shows that the duration of symptoms before the decision to operate is notably longer than the preoperative in-hospital delay, and it supports the assumption that most perforations occur before arriving at hospital.[5] Although the prolongation of symptoms is associated with complicated appendicitis,[2,4] it appears that an additional 8 h in-hospital delay does not increase the risk of perforation. However, post-hoc analyses suggest that there might be a slight increase in perforation rate, although clinically not significant, if preoperative delay is closer to 24 h or longer.

Our results are similar to those from retrospective studies,[2,9,10] in which the prolonged delay was not associated with an increased risk of postoperative complications and morbidity. However, our study did not find an association between prolonged waiting times and incidence of surgical site infection compared with the retrospective study by Teixeira and colleagues.[30] In our study, 122 (7%) of 1802 patients had a postoperative complication within 30 days of surgery. Only 19 (1%) of 1803 patients had the most severe complications requiring invasive treatments, of whom only three had initially complicated appendicitis. Although laparoscopic appendicectomy is a routine procedure, every operation should be performed with special care to minimise postoperative complications.

The study also included patients with CT-verified appendicolith, which is a known risk factor for appendix perforation.[15] The previous assumption was that a longer delay would elevate the risk of perforation in these patients. However, subgroup analysis of these patients showed no significant difference in the perforation rate between the red and orange groups. Nevertheless, the absolute difference was 4·0% and the upper end of two-sided 95% CI was 11·2%. We cannot state that a

longer delay in patients with appendicoliths is non-inferior to a shorter delay because the sample size calculation did not consider this subgroup analysis. Moreover, most patients with appendicoliths did not develop perforations preoperatively. Therefore, appendicolith as an individual risk factor does not classify appendicitis as complicated.

Resources in emergency operating rooms are allocated differently in different hospitals. Some hospitals perform simple appendectomies in the evening and even at night,[18] reserving the operating room capacity for more complex operations during the daytime, whereas other hospitals only perform mandatory surgeries at night.[6] Therefore, this difference in distribution affects how this study's results can be used in practical work in different hospitals. However, the study shows that after postponing the surgery for approximately 14 h, patient safety remained unchanged, and the risk of perforation did not increase while waiting for surgery. This finding indicates that it is safe, for example, to postpone surgery from night-time to daytime in selected patients with appendicitis. Nevertheless, it should be noted that most of the patients were young and relatively healthy (American Society of Anesthesiology grades 1 or 2) and only a few patients used immunosuppressive medication. Therefore, the generalisability of the research results for older patients and patients with immunosuppression must be considered on a case-by-case basis. Additionally, during the waiting period, adequate pain relief for the patients must be given, and possible progressive symptoms should be observed and acted on. From the patient's perspective, it would have been useful to gather more information about how they experienced the longer waiting time and prolonged hospital stay.

This study had some limitations. First, although patients were instructed to contact the surgical unit that performed the surgery in case of any deviation from normal recovery, some minor complications might have been undetected by using the Nationwide Patient Data Repository search. However, it is unlikely that the patient would have been readmitted without our knowledge since all hospitalisations and emergency surgeries performed in the Helsinki University District in Finland are recorded in the same database. In Norway, the operating surgeon completed a complication form for every patient at discharge and 30 days postoperatively. Second, the study was unblinded because of its open-label design. As surgeons assessing the primary outcome were not masked, we cannot exclude possible bias regarding this. However, pathologists were masked to group assignment, and all perforations, except three, were identified by surgeons. Third, patients with more severe symptoms were operated on more urgently than those with mild symptoms. However, because of the limited number of emergency operating rooms, the planned urgency of surgery was not actualised for many patients. This limitation was mitigated by the per-protocol and modified per-protocol analyses, which showed similar results to those of the main intention-to-treat analyses. Additionally, per-protocol analyses did not mitigate the possible short delay in some patients who were randomly assigned to the orange group. However, we considered it unethical to delay surgery for patients in the orange group if an operating room was available. Ultimately, 214 (24%) of 896 patients in the orange group were operated on within 8 h. Fourth, a prespecified absolute non-inferiority margin resulted in a higher relative non-inferiority margin than anticipated due to the lower rate of perforated appendix. However, clinically, a 5% non-inferiority margin is still valid. Fifth, if antibiotics reduce perforation risk, the effect of delay on perforations might be reduced. Conversely, because antibiotics were used with the same frequency in both groups, we do not believe that the antibiotics introduced bias. Sixth, unfortunately, a substantial proportion of patients did not return the numerical rating scale form or filled it in incompletely, which limits the interpretation of pain while waiting for surgery. Last, all patients were adults and presumably selected to have uncomplicated appendicitis; therefore, the results cannot be applied to all appendicitis cases.

No diagnostic method can identify all complicated appendicitis cases before surgery. However, conservative treatments[15–17] have shown that only a small proportion of patients develop perforations. Preoperative scoring[31] and CT increased the diagnostic accuracy. Additionally, the inclusion criteria can be used to assess the perforation risk. Therefore, with appropriate criteria, it would be possible to identify patients at low risk whose surgery can be postponed and even wait for plausible spontaneous resolution of appendicitis.

In conclusion, appendicectomy is the gold standard for treating acute uncomplicated appendicitis, with high efficiency and low complication rates.[1] Since appendicitis remains the most common emergency surgery, our results can be applied in clinical practice, such as treating these patients with daytime surgery, reducing expensive night-time work, and freeing up resources for other urgent emergency surgeries. Notably, in patients with presumed uncomplicated acute appendicitis, appendicectomy scheduled within 24 h did not increase the risk of appendiceal perforation compared with appendicectomy scheduled within 8 h.

Contributors

All authors participated in the design of the trial or were the main organising local investigators at the participating hospitals (or both). The central trial team had access to all the dataset, and local investigators had access to the dataset of patients from their centre. KJ and IS collected data. KJ and PM verified the data and performed statistical analyses. All authors were permitted access to the data if they wished. KJ drafted the manuscript with inputs from PM and VS. All authors accept responsibility to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The collected data or related documents cannot be made available to others because of the restrictions imposed by study permissions and Finnish law.

Acknowledgments

The trial was funded by the Finnish Medical Foundation, Mary and Georg Ehrnrooth's Foundation, Biomedicum Helsinki Foundation, and research funds from the Finnish Government (EVO/VTR/TYH). IS received funding from the Norwegian Agency for antibiotic use. We thank the surgeons and surgical residents for their contributions to patient recruitment and the patients for their participation in the trial.

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