DANISH MEDICAL JOURNAL

Protocol Article

Dan Med J 2021;68(6):A12200917

Peroral versus intravenous post-operative antibiotics after surgery for complicated appendicitis: protocol for a cluster-randomised cluster-crossover non-inferiority study

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Dan Med J 2021;68(6):A12200917

ABSTRACT

INTRODUCTION: Complicated appendicitis increases the risk of post-operative intra-abdominal abscess. Treatment of complicated appendicitis is usually a post-operative course of intravenous antibiotics. A study is needed to confirm the results of retrospective studies showing that a post-operative course of oral antibiotics is not inferior to intravenous antibiotics after laparoscopic surgery for complicated appendicitis.

METHODS: The Per oral versus Intravenous Postoperative Antibiotics after surgery for complicated appendicitis (PIPA) trial will be a prospective, multicentre, cluster-randomised cluster-crossover non-inferiority study designed to test whether a three-day post-operative course of oral antibiotics is non-inferior to a three-day post-operative course of intravenous antibiotics as standard care after laparoscopic surgery for complicated appendicitis in regards to the risk of post-operative intra-abdominal abscess formation within 30 days. Participating hospitals will either be randomised to a six-month period with an oral antibiotic regime followed by a six-month period with an intravenous antibiotic regime for the post-operative treatment after laparoscopic surgery for complicated appendicitis, or to a six-month period with an intravenous antibiotic regime followed by a six-month period with an oral antibiotic regime for post-operative treatment after laparoscopic surgery for complicated appendicitis.

CONCLUSIONS: The primary outcome will be the incidence of intra-abdominal abscess by post-operative day 30.

FUNDING: none.

TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency and by the National/Regional Committee on Health Research Ethics.

According to numbers from the Danish National Patient Register, 6,000 patients undergo surgery for appendicitis in Denmark annually. During the past two decades, laparoscopic appendectomy has replaced open appendectomy as the main surgical treatment of appendicitis in Denmark [1].

Approximately 40% of patients with appendicitis are diagnosed perioperatively with complicated appendicitis

[2]. One example of complicated appendicitis is perforated appendicitis, but no uniform definition exists [3]. Complicated appendicitis increases the risk of post-operative intra-abdominal abscess and wound infections.

It is well established that perioperative intravenous antibiotics reduce the risk of wound infections and intra-abdominal abscesses after surgery for appendicitis [4]. Post-operative treatment with intravenous antibiotics after surgery for complicated appendicitis appears to rest on empirical data. The literature indicates that oral antibiotics are equivalent to intravenous antibiotics, and extending administration of antibiotics by more than three post-operative days does not minimise the risk of intra-abdominal abscess [2, 5, 6]. Consequently, a change in antibiotic regime from intravenous to oral administration will reduce length of stay by 1-2 days and overall cost by 30% equivalent to up to 1,350 € per patient [7].

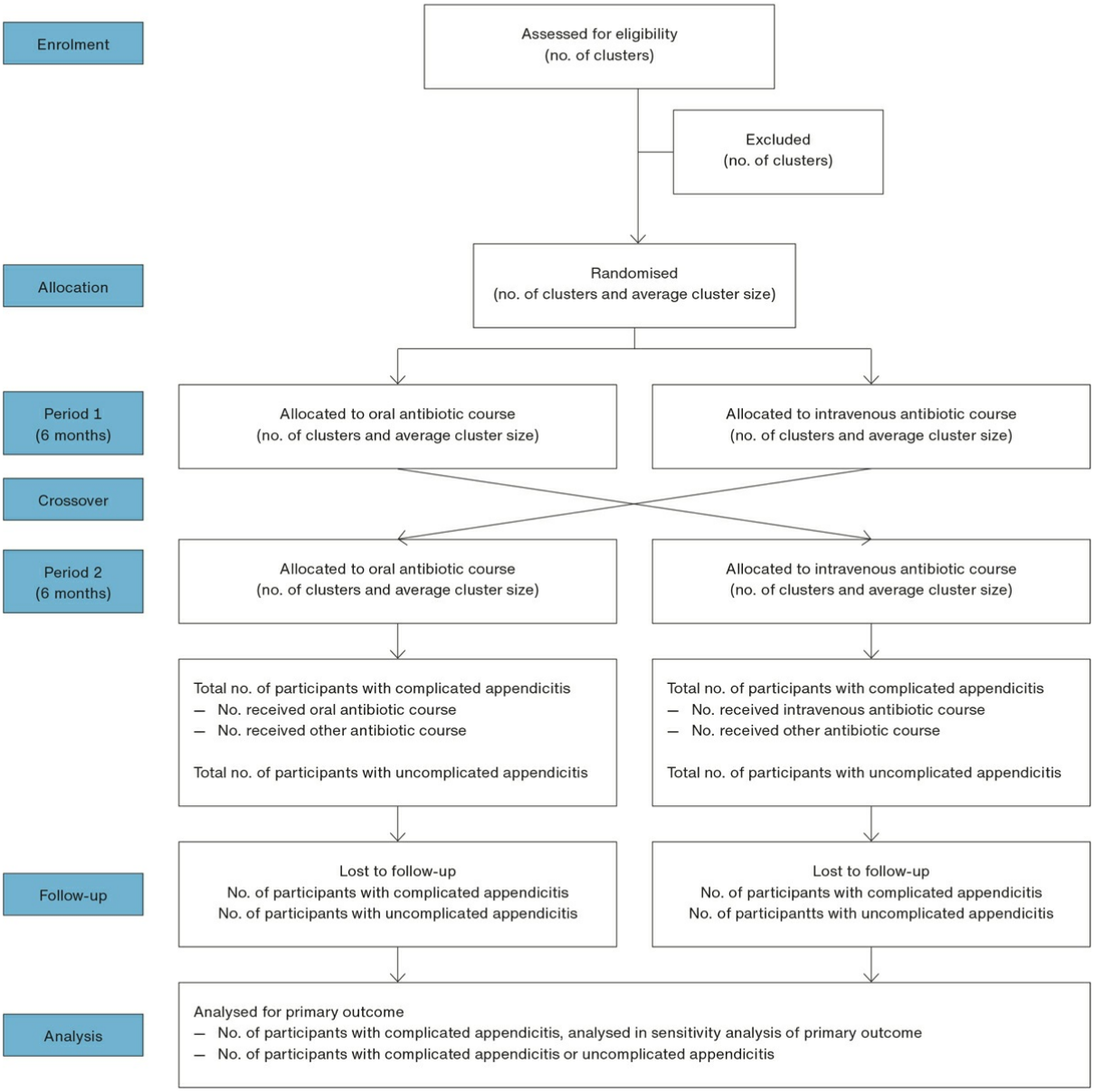
A change of antibiotic regime may affect the surgeon's decision to classify a patient as having uncomplicated or complicated appendicitis. Furthermore, randomised trials have the risk of a low external validity. Therefore, we have chosen to perform a study with a pragmatic design in which hospitals will be randomised to administer oral and then intravenous antibiotics or vice versa for a period of six months as standard treatment of patients with complicated appendicitis in regards to the post-operative antibiotic regime.

The Per oral versus Intravenous Postoperative Antibiotics after surgery for complicated appendicitis (PIPA) trial is a prospective, multicentre, cluster-randomised and cluster-crossover non-inferiority study. We aim to test whether a three-day post-operative course of oral antibiotics is non-inferior to a three-day post-operative course of intravenous antibiotics as standard care after laparoscopic surgery for complicated appendicitis in regards to the risk of post-operative intraabdominal abscess formation within 30 days.

METHODS

The study protocol is reported in accordance with the SPIRIT 2013 Statement [8]. The study is designed as a cluster-randomised and crossover non-inferiority study (**Figure 1**). Detailed methods are included in the **Supplementary appendix (**https://ugeskriftet.dk/files/a12200917_-_supplementary.pdf**)**.

FIGURE 1 Flow diagram of the Per oral versus Intravenous Postoperative Antibiotics after surgery for complicated appendicitis (PIPA) trial.



Study setting

The trial will be conducted in Denmark including ten hospitals from the five Regions of Denmark.

Eligibility criteria

At the cluster level, hospitals with emergency surgical admissions performing laparoscopic appendectomies are eligible for inclusion.

On the individual level, participants are eligible for inclusion if they undergo a laparoscopic appendectomy for appendicitis (both uncomplicated and complicated), are ≥ 18 years of age and provide a signed written consent form. The exclusion criteria are specifically related to the therapy, and individual participants will be excluded if they undergo any other procedures than laparoscopic appendectomy during their index surgery.

Intervention

All participants with appendicitis will receive the same standard treatment of pre- or intraoperative intravenous antibiotics. The three-day post-operative intravenous antibiotic regime will consist of piperacillin/tazobactam and metronidazole. The three-day post-operative oral antibiotic regime will consist of amoxicillin/clavulanic acid and metronidazole (**Table 1**).

TABLE 1 Overview of intervention at cluster level.

		Post-operative course	
Period	**Antibiotics[a] for appendicitis**	**arm 1**	**arm 2**
Pre- or intraoperatively	Single-dose intravenous injection metronidazole 1,000 mg Single-dose intravenous injection piperacillin/tazobactam 4,000 mg/500 mg		
In case of allergy to penicillin	Single-dose intravenous injection metronidazole 1,000 mg Single-dose intravenous injection cefuroxim 1,500 mg		
First 6 post-operative mo.s		Tablet amoxicillin/clavulanic acid 500 mg/125 mg every 8 h for 3 days post-operatively	Intravenous metronidazole 500 mg every 8 h for 3 days post-operatively
		Tablet metronidazole 500 mg every 8 h for 3 days post-operatively *In case of allergy to penicillin*	Intravenous piperacil-lin/tazobactam 4,000 mg/ 500 mg every 8 h for 3 days post-operatively *In case of allergy to penicillin*
		Tablet metronidazole 500 mg every 8 h for 3 days post-operatively	Intravenous metronidazole 500 mg every 8 h for 3 days post-operatively
		Tablet ciprofloxacin 500 mg every 12 h for 3 days post-operatively	Intravenous cefuroxim 1,500 mg every 8 h for 3 days post-operatively
		No further antibiotics due to uncomplicated appendicitis	No further antibiotics due to uncomplicated appendicitis
Final 6 post-operative mo.s		Intravenous metronidazole 500 mg every 8 h for 3 days post-operatively	Tablet amoxicillin/clavulanic acid 500 mg/125 mg every 8 h for 3 days post-operatively
		Intravenous piperacillin/tazobactam 4,000 mg/ 500 mg every 8 h for 3 days post-operatively *In case of allergy to penicillin*	Tablet metronidazole 500 mg every 8 h for 3 days post-operatively *In case of allergy to penicillin*
		Intravenous metronidazole 500 mg every 8 h for 3 days post-operatively	Tablet metronidazole 500 mg every 8 h for 3 days post-operatively
		Intravenous cefuroxim 1,500 mg every 8 h for 3 days post-operatively	Tablet ciprofloxacin 500 mg every 12 h for 3 days post-operatively
		No further antibiotics due to uncomplicated appendicitis	No further antibiotics due to uncomplicated appendicitis

a) Both uncomplicated and complicated.

Table 1 has been updated on June 3rd 2021.

Complicated appendicitis is defined as perforated appendicitis (including periappendicular abscess), appendicitis with diffuse purulent peritonitis, gangreanous appendicitis and post-operative treatment with antibiotics prescribed by the surgeon that is not due to the before-mentioned factors. Patients will be classified at the discretion of the surgeon in charge as having uncomplicated appendicitis or complicated appendicitis. Patients with uncomplicated appendicitis receive no additional antibiotics, whereas patients with complicated appendicitis receive a three-day post-operative antibiotics course. All patients who are prescribed a three-day post-operative antibiotics course are registered as having complicated appendicitis and patients not prescribed antibiotics are registered as having uncomplicated appendicitis.

The treating physician may prescribe a different post-operative antibiotic regime than the standard regime at any time if circumstances indicate the use of other antibiotic regimes.

Adherence to the treatment protocol will be assessed at post-operative day 3-5 by telephone contact to participants undergoing outpatient therapy and by extraction of information from electronic medical records from inpatient participants.

Outcomes

The primary outcome will be the incidence of intra-abdominal abscess by post-operative day 30. The primary outcome is defined as an imaging-verified intra-abdominal mass treated with drainage or antibiotics, or a surgically verified intra-abdominal abscess within 30 post-operative days. The secondary outcomes are post-

operative length of stay in hours, complications according to the Clavien-Dindo Classification at post-operative day 30 that require in- or outpatient treatment, complications of grade ≥ 3a according to the Clavien-Dindo Classification at post-operative day 30, inpatient costs at post-operative day 30, outpatient cost at post-operative day 30, overall cost of both in- and outpatient treatments at post-operative day 30 and post-operative wound infections that require in- or outpatient treatment. A wound infection is defined as a clinically suspected wound infection that has been treated with an opening of the wound or where antibiotics have been administered for this indication by post-operative day 30.

Sample size

The risk of intra-abdominal abscess is 7% in patients who undergo appendectomy due to a complicated appendicitis [2]. At a power of 90%, a significance of 5% and using a non-inferiority margin of 5%, 447 patients with complicated appendicitis are required in each group to determine that oral antibiotic treatment does not increase the risk of intra-abdominal abscess by more than 5% (from 7% to 12%) after a laparoscopic appendectomy for complicated appendicitis. We have chosen a pre-specified non-inferiority margin of 5%. One ongoing trial has also pre-specified the non-inferiority margin to 5%, demonstrating that our results are in conformity with those of other authors [9].

In order to maintain a power comparable to that of an individually randomised trial, the number of participants in a cluster-randomised trial must be increased. The intraclass correlation coefficient (ICC) is relevant to define the desired increase in the number of participants, and it can be calculated by the variance inflation factor (VIF) [10]:

VIF = 1 + (sample size in each arm at an individual RCT – 1) × ICC

From a former retrospective study with four hospitals and a total population of 1,141 patients, the ICC was calculated as –0.001703743 [2]. If ICC is estimated to be a negative number, it may be defined as zero or a very small positive number. Since our study includes cluster-level crossover, we have assumed an ICC of zero. The total sample population should therefore be the same as in an individualised clinical trial [11].

In a cluster-randomised trial, it is important to determine the total of clusters in order to maintain power of the study. The number of clusters must be higher than the total number of participants multiplied by the ICC. We have determined that ten clusters are required for our study and the enrolment duration will last *until* 500 patients with complicated appendicitis have been included in each group. With this approach, we are able to accomplish a per-protocol and intention-to-treat analysis. We do not anticipate loss-to-follow-up. Although we expect that about 10% of patients will go through a change in their antibiotics regime and deviate from the protocol [2].

Assessment of selection bias will be handled by performing a sensitivity analysis of the entire sample of patients with appendicitis. With an anticipated inclusion of 1,000 patients due to complicated appendicitis, we expect that a total of 2,631 patients will be included with appendicitis of whom 1,631 will have uncomplicated appendicitis. The incidence of intra-abdominal abscess is estimated to be 2.6% (0.07 × 0.38) in the entire sample of patients with appendicitis. With a non-inferiority margin of 1.9% (0.05 × 0.38), a significance level of 0.05 and a power of 90%, a total of 1,202 patients are needed in each group.

Randomisation

An electronic randomisation sequence in the program R will be applied to randomise centres (clusters) 1:1. After randomisation, the allocation will not be concealed.

Data collection and management

The following data will be registered prospectively and extracted retrospectively through patients' medical records: sex, date of birth, date and time of start and conclusion of surgery, American Society of Anesthesiologists (ASA) class, date and time of hospital admission, date and time of discharge, reason for classifying the appendicitis as complicated, compliance according to protocol regarding administration of standard treatment, change of antibiotic regime within three post-operative days defined by a change from oral to intravenous treatment, a change from intravenous to oral treatment, administration of different either oral or intravenous antibiotics, extended therapy with antibiotics for more than three days, post-operative complications at post-operative 30 day according to the Clavien-Dindo Classification of Surgical Complications and the Comprehensive Complication Index and specifically intra-abdominal abscess, wound infection and re-admissions.

From the Danish Health Authority, data about hospital and general practice sector costs are extracted at post-operative 30 day. The amount will be presented in euro currency using the exchange rate recorded on the day of crossover for the first cluster.

Data will be recorded into a pre-established Research Electronic Data Capture (REDCap) database. The data will be stored in agreement with the guidelines of the Danish Data Protection Agency. Electronic data will be stored for five years after the end of the study and will subsequently be transferred to and stored in the Danish Data Archive.

Statistical methods

Baseline data will be presented as median (interquartile range) or numbers (percentage) and absolute mean difference between the two groups unless otherwise stated.

The primary and secondary outcomes will be analysed for participants with complicated appendicitis. In order to assess selection bias/confounding by indication, a sensitivity analysis of the primary outcome will be performed for all participants (both uncomplicated and complicated appendicitis).

Data will be analysed at the level of the individual, but clustering will be taken into account. To assess binary outcomes, we will use a generalised estimating equation (GEE) based on robust estimator, exchangeable covariance and a logit link function. For continuous data, the GEE analysis will be used, which is based on robust estimator, exchangeable covariance and an identity link function. Intention-to-treat and per-protocol analyses will be included and both are required in a non-inferiority study. Interim analyses are not planned. A p-value of ≤ 0.05 is considered significant.

All available data will be applied and in case of missing data, appropriate imputation strategies will be applied according to the recommendations from *the Copenhagen Trial Unit* [12].

Assuming inverse probability, treatment weighting is required; cluster, age, gender, ASA, pathology report and duration of surgery will be included in the propensity score. The balance between the applied covariates will be controlled [13].

Trial registration: The study was approved by the Danish Data Protection Agency and by the National/Regional Committee on Health Research Ethics.

DISCUSSION

Our study is designed as a cluster-randomised and cluster-crossover non-inferiority study. We have chosen to randomise at cluster level in order test the use of a standard treatment in a real clinical setting. Our study is a pragmatic trial; compared to an experimental trial, it therefore tries to strike a balance between internal and

external validity. A pragmatic trial aims to strengthen external validity, and a possible liability is that internal validity is weakened as a result. Cluster-randomised trials carry a risk of selection bias as individual participants are recruited after randomisation. However, in our trial, inclusion will not affect treatment of the patient, and the risk of selection bias should be negligible. A risk exists that the allocated treatment may affect the decision to classify patients as having complicated appendicitis and to prescribe the allocated antibiotic course. Sensitivity analyses are useful in gathering a good overview of the potential biases and will help us adjust accordingly [14]. By performing a sensitivity analysis of the primary outcome on all patients with appendicitis, we safeguard our study against the above intermediate between-selection bias and confounding by indication.

The cluster variation in a previous retrospective study including many of the clusters eligible for inclusion showed almost no variation between clusters. Furthermore, the use of a crossover design should reduce the effect of cluster variation if any is present. No carry-over effects are likely to occur in this crossover trial [15]. We have chosen a non-inferiority margin of 5%. The margin is selected on a clinical basis; and due to the lack of historical data, we cannot justify it based on statistical considerations.

Our hypothesis is that oral antibiotic post-operative treatment is non-inferior to intravenous antibiotic treatment after laparoscopic appendectomy due to complicated appendicitis. Treatment with oral antibiotics will yield a significantly shorter length of stay and a reduction in overall healthcare costs.

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Accepted 12 April 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the full text of this article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(6):A12200917

Correction: Table 1 has been updated on June 3rd 2021.

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