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Supplementary Appendix

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Detailed methods and statistical analysis

Intervention

A retrospective study demonstrated that treatment with oral antibiotics is non-inferior to intravenous antibiotics for patients with complicated appendicitis[1].

Many studies have demonstrated especially for pneumonia and urinary tract infection that converting from intravenous antibiotic regime to oral antibiotic regime is safe as long as the patient is in stable clinical state[2][3]. Benefits from changing from intravenous to oral antibiotics include reduction in cost, reduced risk of catheter complication and a simple route of administration. The most common used antibiotics has one or more oral options with a high bioavalability and particularly for amoxicillin and metronidazole[4].

In clinical guidelines, metronidazole single-handedly is not recommended for treatment of both uncomplicated and complicated appendicitis. A combination of cephalosporin, piperacillin together with metronidazole is typically recommended[5]. Ciprofloxacin, a second generation wide activity fluoroquinolone, is active against both Gram-negative and Gram-positive bacteria. Ciprofloxacin is often combined with metronidazole, and metronidazole has a good anti-anaerobic activity[6]. The most frequent microorganisms are aerobic and anaerobic gram-negative enteric organisms. E.coli is the most recurrent aerobe organism, and Bacteroides fragilis is the most frequent anaerobe suggesting that the bowel flora represent a key origin for infectious microorganism. Other microorganism have been documented such as Pseudomonas aeuroginosa, Staphylococcus and Enterococcus groups[5].

The intraoperative reason for prescribing a postoperative course of antibiotics are registered by the following categories: perforated appendicitis (including appendicitis with periappendicular abscess), appendicitis with diffuse purulent peritonitis, gangrenous appendicitis, or other causes than the above mentioned.

For patients receiving oral treatment the pills will be distributed to them by staff personnel before discharge and undergoing outpatient antibiotic treatment.

Participant timeline

Potentially eligible participants suspected of appendicitis and scheduled for laparoscopic surgery are asked to participate in the trial and either accepts by oral and written consent or declines participation prior to surgery. Participating in this study is dependent on obtaining the patients approval. In every centre a screening- and inclusion list is maintained. If patients decline to participate their initials will be registered on a screening list. By accepting their initials and personal identification number are registered on an inclusion list. Depending on randomization, every cluster will administer the antibiotic regime as their standard treatment for patients who undergo laparoscopic appendectomy due to appendicitis, regardless of patient participation, since the allocated treatment is standard treatment.

Sample size calculation for secondary outcomes

In an attempt to show that per oral antibiotics reduces postoperative length of stay with a minimum of 24 hours (lower limit 95% CI), then 158 patients are required in each arm (average length of stay in IV group at 93 hours, average length of stay in PO group at 35 hours, standard deviation at 103 hours, level of significance at 5% and a power of 90%)[1].

In an attempt to demonstrate that per oral antibiotic regime does not increase the relative risk for serious complications such as grade ≥ grade 3a according as per Clavien-Dindo Classification of Surgical Complications[7] by more than 5% (from 12% to 17%) 523 patients is needed in each group (level of significance 5% and a power of 80%)[1].

The risk of wound infections is about 1% after laparoscopic appendectomy caused by complicated appendicitis[1]. To demonstrate that per oral antibiotic administration postoperative does not increase the absolute risk of wound infections by more than by more than 2% (from 1%to 3%), 424 patients are required in each arm (level of significance 0.05 and a power of 90%)

The average diagnosis related groups (DRG) for a male, 32 years old, admitted to hospital for 4 days with complicated appendicitis (postoperative 3 days) and have performed laparoscopic appendectomy is 4535 €. By an average reduction of 1344 € with each admitted patient treated of

complicated appendicitis, and a presumed standard deviation of 2284 €, then 76 patients are needed in each group (level of significance 0,005 and a power of 95%). With 500 patients in each group and with the above mentioned assumptions, then we expect to determine a difference of minimum 537 € per patient.

Recruitment

In order to increase the success of recruiting clusters, we have documented a comprehensive list containing key personnel at every cluster. Names on this list will be contacted by coordinating principal investigator and sponsor by phone, email or face-to-face-meeting. The list contains names from relevant emergency surgical departments, key research personnel such as head of research and other principal investigators that will oversee the data management at each cluster. At individual level the clinician team will prior to surgery affirm the eligibility criteria. Patients will be introduced to the study by being presented with oral and written consent.

Ethics and dissemination

The sponsor initiated the study and the sponsor has no affiliation with funding sources. Involved hospitals and The Regional Committee on Health Research Ethics will be informed in the event that new financial support materialize, and we will include the name of the source, amount and the sponsors' affiliation with the financial provider. After conferring with Danish Health and Medicines Authority no approval from Danish Health and Medicines Authority was needed. The study is approved by the Danish Data Protection Agency, National/Regional Committee on Health Research Ethics. The trial will be listed on Clinicaltrials.gov.com. Information about the study participants is protected according to national data safety laws.

The patient is asked to participate prior to surgery and accepts or declines before the time of surgery. The information and obtaining consent will be by the doctor involved in the acute patient care at the emergency surgical department. The communication between the patient and the doctor will take place in hospital.

The written consent is provided to the patient after the oral information is delivered. The patient is informed that they can have a representative during the oral information, and if they choose to have a representative present, the information will only be delivered as long as the representative is present. The study will be presented in plain language and will be adjusted to the relevant participant in terms of age, maturity and experience. The participants are informed about the following: All eligible patients are requested to participate in the study, the study investigates whether 2 standard treatments are non-inferior in comparison following laparoscopic appendectomy, their entry into the study will have no impact on their treatment, in case the patient declines they will still receive the current standard treatment, information from their medical records will be extracted, all patients are free to withdraw their consent and ask to drop-out of the study for any purpose and at any time, and it is within the participants right to have a representative present during the oral information.

Individual participants registered into the study are covered by indemnity negligent harm by means of the Danish Healthcare Service.

Positive, negative and inconclusive results will be published. Results will be published in agreement with relevant CONSORT extensions[8][9]

Any adverse events will be registered as usual since the treatment administered is standard treatment. Postoperative complications will be registered according to Clavien-Dindo Classification of Surgical Complications and the Comprehensive Complication Index [10][7].

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