University of Thessaly

Health Science School

Department of Human Medicine

Postgraduate Program (Msc)

''Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics''

Master of Science Thesis

''Protocol for a superiority phase III RCT for assessing the effectiveness of antibiotics versus surgery for treating pediatric acute uncomplicated appendicitis.''

''Πρωτόκολλο φάσης III RCT για την εκτίμηση της αποτελεσματικότητας των αντιβιοτικών έναντι εγχείρησης για την αντιμετώπιση οξείας ανεπίπλεκτης σκωληκοειδίτιδας στα παιδιά.''

Postgraduate Student: Mylona Charitini

Supervisor: Doxani Ch.

Stefanidis I.

Zintzaras E.

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Table of Contents

SYNOPSIS

Title	Antibiotics versus surgery for treating pediatric acute uncomplicated appendicitis.
Study Design	Phase III Randomized Control Trial.
Study Participants	Children 6-16 years old.
Sample Size	74 children (37 randomly distributed to each group)
Planned Study Period	September 2019 – September 2021.
Primary objectives	NOM success rate: proportion of children with the diagnosis of AUA undergoing only antibiotic treatment with no need for appendectomy within hospitalization or follow up period.
Secondary objectives	• Length of hospital stay. • Number of days absent from school, social or sport activities. • Complications. • Recurrent appendicitis within 6 months of randomization.
Interventions	• IV ceftriaxone + metronidazole for 48-72 hours. • If clinical deterioration within the first 24 hours patients will be subjected to appendectomy. • Patients will be discharged when asymptomatic with a 5 day PO antibiotic course: ciprofloxacin + metronidazole.
Comparator	Three port laparoscopic

	appendectomy.

1.0 Abbreviations

NOM	Non-operative management
AUA	Acute Uncomplicated Appendicitis
AA	Acute Appendicitis
WBC	White Blood Cell
CRP	C Reactive Protein
US	Ultrasound
IN	Intravenous
PO	Per Os
NPO	Nothing Per Os
SUR	Surgery
IRB	Institution Review Board
CRF	Case Report Form
(S)AE	(Serious) Adverse Event
IP	Investigational Product

2.0 Abstract

Background

Appendectomy for acute uncomplicated appendicitis has recently been questioned as being the only correct treatment. Appendectomy has been reported to have significant early and late morbidity. This can be avoided with antibiotic treatment alone. However conclusive evidence with regard to the efficacy of antibiotic treatment alone in children with proven acute appendicitis is lacking.

Objectives

The aim of this study is to evaluate the effectiveness and safety of non-operative treatment of acute uncomplicated appendicitis with antibiotics in children of age 6 to 16 years old.

Methods

During September 2019- September 2021, children with radiologically and clinically diagnosed acute uncomplicated appendicitis will be randomized either to treatment with antibiotics or to laparoscopic appendectomy. Key points of this protocol will be antibiotics, appendicitis, children, surgery as well as randomized control trial. Categorical data will be tested using the x^2 test. Non-parametric data will be analyzed using the Mann Whitney U test for continuous variables and the Fisher's exact test for categorical variables.

Results

The primary endpoint for this study will be the non-operative management success rate. Secondary endpoints will be: length of hospital stay, complications such as gangrenous or perforated appendicitis, allergic reaction to antibiotics, abscess formation, wound infection as well as recurrent appendicitis within 6 months of randomization. Also, parental satisfaction will be addressed.

Conclusions

Treating acute unperforated appendicitis in children with antibiotics alone is promising. However, their effectiveness and effect on quality of life have yet to be established in an adequately powered randomized trial.

Εισαγωγή

Η σκωλικοειδεκτομή έχει πρόσφατα αμφισβητηθεί για το αν αποτελεί τη μοναδική θεραπεία για την αντιμετώπιση της οξείας ανεπίπλεκτης σκωλικοειδίτιδας καθώς έχει αναφερθεί να κατέχει σημαντικά υψηλή τόσο πρώιμη όσο και όψιμη νοσηρότητα. Αυτό μπορεί να αποφευγθεί με τη χρήση αντιβιοτικών ως μονοθεραπεία για την αντιμετώπιση της οξείας σκωλικοειδίτιδας. Εντούτοις, δεν υπάρχουν ισχυρά αποδεικτικά στοιχεία σχετικά με την αποτελεσματικότητα της αγωγής μόνο με αντιβιοτικά σε παιδιά με αποδεδειγμένη οξεία σκωληκοειδίτιδα.

Στόχοι

Ο βασικός στόχος αυτής της μελέτης είναι η εκτίμηση της αποτελεσματικότητας και της ασφάλειας της μη επεμβατικής θεραπείας σε παιδιά με οξεία ανεπίπλεκτη σκωληκοειδίτιδα ηλικίας 6-16 ετών.

Μέθοδοι

Κατα τη διάρκεια της περιόδου Σεπτέμβριος 2019- Σεπτέμβριος 2021 , παιδιά με ακτινολογικά και κλινικά διαγνωσμένη οξεία ανεπίπλεκτη σκωληκοειδίτιδα θα κατανεμηθούν τυχαία ώστε να λάβουν είτε αντιβιοτικά είτε να υποβληθούν σε λαπαροσκοπική σκωληκοειδεκτομή. Σημεία κλειδιά αυτού του πρωτοκόλλου θα είναι :αντιβιοτικά, σκωληκοειδίτιδα, παιδιά, επέμβαση καθώς και τυχαιοποιημένη κλινική μελέτη. Τα κατηγορικά δεδομένα θα μελετηθούν με το τεστ x^2 . Τα μη παραμετρικά δεδομένα θα αναλυθούν με τη χρήση του Mann Whitney U τεστ για τις συνεχείς μεταβλητές και με το Fischer’s τεστ για τις κατηγορικές μεταβλητές.

Αποτελέσματα

Το κύριο αποτέλεσμα αυτής της μελέτης θα είναι το ποσοστό επιτυχίας της μη επεμβατικής θεραπείας. Τα δευτερεύοντα αποτελέσματα θα είναι : η διάρκεια νοσηλείας, αλλεργικές αντιδράσεις στα αντιβιοτικά, σχηματισμός αποστήματος, μόλυνση του τραύματος καθώς και η επανεμφάνιση της σκωληκοειδίτιδας στους πρώτους 6 μήνες απο την τυχαιοποίηση. Επίσης, θα εκτιμηθεί η ικανοποίηση των γονέων.

Συμπέρασμα

Η αντιμετώπιση της οξείας αδιάτρητης σκωληκοειδίτιδας σε παιδιά μόνο με αντιβιοτικά είναι πολλά υποσχόμενη. Ωστόσο, η αποτελεσματικότητά τους

και η επίδρασή τους στην ποιότητα ζωής οφείλει να ελεγχεί σε μια κατάλληλα δοκιμασμένη τυχαιοποιημένη κλινική δοκιμή.

3.0 Background

The lifetime risk of developing appendicitis is approximately 9%, and with 300,000 cases diagnosed annually in the US, appendectomy represents the most common urgent abdominal procedure in children and adults (1, 2). Laparoscopic appendectomy is now considered the standard operation for uncomplicated acute appendicitis (UAA) and patients are often discharged directly from the recovery room. This procedure has minimal complications and also enables early return to school, sports and daily activities (3-7). Despite the favorable outcomes seen after laparoscopic appendectomy, a nonoperative trend for the treatment of UAA has recently emerged. This paradigm shift is mainly driven by the desire to minimize negative appendectomy rates and avoid potential risks associated with surgery and anesthesia (8-10).

Champions of nonoperative management (NOM) frequently refer to this approach as conservative treatment to highlight its non-invasive nature. However, concerns have been raised about whether there is evidence of non-inferiority over laparoscopic appendectomy to be offering it to patients as an alternative to the current standard of care (11, 12). With recent studies in adults showing a 36.2% one-year failure rate and a 45% eight-year failure rate for NOM of UAA, increasingly more clinicians are questioning the appropriateness of this strategy (13, 14).

The evidence on non-surgical management of uncomplicated acute appendicitis in pediatric patients is even less robust.

4.0 Methods

4.1 Study design

This investigation will be designed as a phase III randomized control trial comparing NOM (antibiotics) and surgery for AUA in children. Blinding is not feasible. It will be conducted at the G. Genimatas General Hospital of Thessaloniki from September 2019 until September 2021. All patients with radiologically and clinically diagnosed AUA will be screened for inclusion in the study. Age, sex, duration of symptoms, body temperature, C-reactive protein as well as white blood cell will be recorded at admission.

4.2 Study Participants

Eligible for inclusion will be children 6-16 years old of both sexes, in whom an imaging-confirmed AUA is diagnosed in the emergency department and who would have been subjected to an appendectomy before the trial.

4.2.1 Inclusion Criteria

- Age 6-16 years, both male and female.
- Clinical findings suspicious for AA:

-Unwell, but not generally ill.

- Localized tenderness in the right iliac fossa region.

-Normal/hyperactive bowel sounds.

-No palpable mass or guarding.

-Duration of symptoms < 48h.

- Radiologically confirmed simple AA defined as:
  US:

  -Incompressible appendix with max diameter of ≥ 6mm.

  -Hyperemia within the appendiceal wall.

  -Periappendicial fluid.

  -Increased echogenicity of periappendiceal fat.

  -No signs of perforation.

  - No signs of intra-abdominal abscess/phlegmon.

In case the ultrasound is inconclusive, additional imaging (MRI or CAT scan) may be obtained.

- Laboratory findings :
- WBC > 12.000/μL
- CRP > 3 mg/dL.
- Body temperature > 37 ◦C and < 38 ◦C.

4.2.2 Exclusion Criteria

- Duration of symptoms > 48 hours.
- Clinical and/or radiographic evidence of perforated appendicitis.
- Generalized peritonitis or sepsis.
- Presence or suspicion of abscess or phlegmon on imaging.
- US evidence of appendicolith.
- Serious comorbidity such as cardiac or pulmonary disease with significant hemodynamic consequences, immunodeficiency, malignancy or sickle cell disease.
- Suspicion of an underlying malignancy or inflammatory bowel disease.
- A history of non-operatively treated appendicitis.
- Documented type 1 allergy to the antibiotics used.
- Inability to return quickly to the hospital if symptoms persist or recur.

4.3 Randomization

Allocation to groups (1:1 ratio) will be made via weighted minimization at the time of enrollment in the study using the following criteria: age (6-10 years or 11-16 years) and sex (male or female). All factors will be weighted equally. Randomization is going to be performed using a computer based randomization program which will allow complete concealment of randomization sequence.

4.4 Blinding

As this is a randomized control trial comparing surgery and NOM with antibiotics it is not considered possible or ethical to blind patients, parents or surgeons.

4.5 Interventions

4.5.1 Antibiotics protocol

NPO for the first 12 hours.

Antibiotic treatment starts with IV ceftriaxone (50 mg/kg/day) and metronidazole (30 mg/kg/day).

In the presence of amelioration of clinical signs and symptoms, surgery will be delayed and this course of antibiotics will be given for 48-72 hours.

If there is clinical deterioration within the first 24 hours patients will be subjected to appendectomy.

Signs and symptoms of clinical deterioration are defined as: increasing levels of WBC and / or CRP, persistent and /or increasing abdominal pain /fever, signs and symptoms of perforated appendicitis and /or sepsis.

Patients will be discharged when they meet the discharge criteria with a 5 day PO antibiotic course: ciprofloxacin (20 mg/kg x 2/ day) and metronidazole (20mg/kg/day).

Discharge criteria:

- Clinically asymptomatic.
- Adequate oral intake.
- Able to mobilize.
- Decreased leukocytosis.
- Decreased CRP.
- No signs of complicated appendicitis on following US.
- Parental consent for discharge.

To optimize early detection of NOM failure, a physician will reassess the patient twice in a daily basis and WBC and CRP will be measured every 24 hours during the time of administration of IV antibiotics. After the first 48 hours, the abdominal US will be repeated to check for signs of complicated appendicitis.

4.5.2 Antibiotics regime

For the primary IV antibiotic course the antibiotics administered are:

1. Ceftriaxone: is a third-generation cephalosporin with broad-spectrum gram-negative activity. It has lower efficacy against gram-positive organisms but higher efficacy against resistant organisms. Ceftriaxone's bactericidal activity results from inhibiting cell-wall synthesis by binding to one or more penicillin-binding proteins and exerts antimicrobial effect by interfering with synthesis of peptidoglycan (major structural component of bacterial cell wall). Bacteria eventually lyse because activity of cell-wall autolytic enzymes continues while cell-wall assembly is arrested.
   Brand name: *Rocefin*.
   Ceftriaxone is often administered to intra-abdominal infections (complicated, mild to moderate, community acquired) in combination with metronidazole.

2. Metronidazole: Inhibits nucleic acid synthesis by disrupting DNA and causing strand breakage.
   Brand name: *Flagyl.*

For the 5 day PO antibiotic course the antibiotics administered are:

3. Ciprofloxacin: belongs to a class of drugs called quinolone antibiotics. It works by stopping the growth of bacteria with the following mechanism of action: inhibits DNA gyrase in susceptible organisms and promotes breakage of double-stranded DNA.
   Brand name: *Cipro, Cipro XR, ProQuin XR.*

4. Metronidazole.

4.5.3 Surgery Protocol

Preoperative antibiotics will be administered to the patient 24h before the surgery:

IV metronidazole (20 mg/kg) for prophylaxis.

Three port laparoscopic appendectomy is the scheduled surgery.

Intravenous fluids weight adjusted and pain medication will be administered according to the same protocol as the NOM group.

4.6 Endpoints

4.6.1 Primary Endpoints

The primary endpoint of this trial is the NOM success rate which is defined as the proportion of children with the diagnosis of AUA undergoing only antibiotic treatment with no need for appendectomy within hospitalization or follow up period.

4.6.2 Secondary Endpoints

-Length of hospital stay.

-Number of days absent from school, social or sport activities.

-Complications.

- Complications due to the antibiotics.
  - Allergic reaction or allergic shock.
  - Gastrointestinal symptoms (vomiting, diarrhea) with the need for treatment.
- Complications due to delayed appendectomy :
  - Gangrenous or perforated appendicitis.
  - Peritonitis.
  - Intra-abdominal abscess.
- Complications related to surgery:
  - Wound infection
  - Intra-abdominal abscess.
  - Secondary bowel obstruction.
  - Need for second operation.
  - Anesthesia related complications.

-Recurrent appendicitis within 6 months of randomization.

4.7 Follow up Protocol

For the NOM group patients will be seen by the attending surgeon one month and one year after the antibiotics treatment, whereas the patients of the control group (laparoscopic appendectomy) will be seen and examined one month, three months and one year postoperatively.

Late complications and readmissions will also be recorded.

4.8 Adverse events

An AE is any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with the investigational drug. An AE can, therefore, be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality that occurs during or after administration of an IP whether or not considered related to the IP.

Adverse events include:

• Symptoms described by the patient or signs observed by the Investigator or medical staff.

• Test abnormalities (laboratory tests, ECG, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at Screening are considered AEs only if they reoccur after resolution or worsen during the AE collection period.

4.8.1 Serious Adverse Events

A SAE is defined as any AE that results in any of the following:

• Death.

• Life-threatening event.

• Required or prolonged inpatient hospitalization.

• Persistent or significant disability/incapacity.

• Congenital anomaly/birth defect.

• Important medical events.

4.8.2 Severity of Adverse Events

The Investigator will assess the severity of all AEs as Mild, Moderate, or Severe, based on the following definitions:

- Mild: The event does not interfere with the patient's usual activities.
- Moderate: The event interferes with the patient's usual activities.
- Severe: The event prevents the patient from undertaking their usual activities and requires therapeutic intervention or cessation of the study treatment.

4.8.3 Collection and Reporting of Adverse Events

Over the entire duration of the study, site personnel will ensure that all AEs are recorded appropriately. If an AE occurs, the primary concern is for patient safety, and the Investigator will use his/her judgment and expertise to determine the appropriate course of action. All AEs from the time of informed consent/assent through the last follow-up visit will be recorded in each enrolled patient's CRF.

For patients who are found to be ineligible for the study during the Screening period and are not enrolled only SAEs will be reported.

If, at any time after the patient has completed participation in the study, the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly/probably or definitely related to the IP or is possibly/probably or definitely related to a study, then the event and any known details must be reported promptly to the Sponsor.

4.9 Overdose

An overdose is not an AE. An overdose will be reported even if it does not result in an AE. An overdose will be recorded on the appropriate form and sent to the Sponsor or designee within 24 hours.

4.10 Withdrawal

Patients can withdraw from the study at any time without explanation. In case of withdrawal, the patient will be treated with an appendectomy.

5.0 Statistical Analysis

Categorical variables will be characterized using frequencies and percentages. Continuous variables will be described as means and standard deviations or if the data are skewed, as medians with 25th and 75th percentiles. Statistical significance for categorical data will be tested using the Pearson chi square test. Non-parametric data will be analyzed using the Mann Whitney U test for continuous variables and the Fisher's exact test for categorical variables. The level of statistical significance will be set at $p < 0.05$. Statistical analysis will be performed using the IBM SPSS Statistics 23.0 program.

6.0 Sample Size

Based on an expected 1-year success rate of NOM of 80%, 37 patients treated nonoperatively were needed to have a 95% confidence interval with a lower limit of 65%, based on the exact binomial distribution. The 65% lower limit was considered the lowest acceptable 1-year success rate to offer NOM to patients in clinical practice. As a result, the sample size is 74 patients, 37 randomly distributed to the NOM group and 37 to the SUR group.

7.0 Data Monitoring Plan

The postgraduate research fellow will be responsible for data collection and tabulation. Furthermore, the research fellow will monitor the progress of the clinical study including ensuring the safety of all patient data and coordinating all involved parties, so that the study may be conducted, recorded and reported in accordance with the protocol, good clinical practice and the applicable regulatory requirements.

8.0 Patient Confidentiality

Each patient will be issued a unique patient identification number and all non-clinically relevant personal information would be neither recorded nor published. The research fellow would be responsible for maintaining patient anonymity and confidentiality. All electronic and print medical records would remain on site in secure G. Genimatas General Hospital of Thessaloniki locations.

9.0 Ethics

Institution review board (IRB) approval would need to be obtained prior to launching the study. Any changes in the study protocol, informed consent forms, or contributing investigators will warrant re-approval by the IRB. This study will be executed in accordance with the Declaration of Helsinki [22] and in line with the E6 Good Clinical Practice: Consolidated Guidance. [23]

10.0 Informed Consent

Proxy informed consent would need to be signed by both biological parents or adoptive parents or court-appointed legal guardians as applicable. Proxy informed consent only from one parent would suffice when the other parent is dead, legally incompetent, not reasonably available, or not legally responsible for the child's care. Emancipated underage patients are considered legally competent to consent for themselves. Assent will be requested from non-emancipated patients if they are at least 7 years old and exhibit appropriate understanding of the process they will undergo. [24]The above described inclusion and exclusion criteria were designed to ensure the entry of the appropriate population of patients to this study and will need approval by the IRB.

Eligible patients and their families will be educated about the research protocol by the research fellow and the supervising G. Genimatas General Hospital of Thessaloniki faculty. All questions would be addressed prior to enrolment. Consent can be withdrawn at any time during the course of the study.

A written informed consent form will be generated. Also, a CRF, providing general medical history, will be filled for every patient included in the study.

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12.0 Appendix A: Study Flow Chart