Supplemental Online Content

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Supplement 2. Statistical analysis plan

This supplemental material has been provided by the authors to give readers additional information about their work.

APPAC II trial: Statistical analysis plan

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Responsibilities:

Approved by Saija Hurme 27.10.2015 / amendment 2.4.2020

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SAS-programming will be done by Teemu Kemppainen.

1. Introduction

APPAC II trial is a multicentre, open-label, non-inferiority randomized controlled trial comparing per oral (p.o.) antibiotic monotherapy with intravenous (i.v.) antibiotic therapy followed by p.o. antibiotics in the treatment of CT-scan confirmed uncomplicated acute appendicitis. Primary endpoint is the success of the randomized treatment, defined as resolution of acute appendicitis resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during one-year follow-up. Secondary endpoints include post-intervention complications (possible postoperative complications classified using primarily the Clavien-Dindo classification[1]), late recurrence (after one year) of acute appendicitis after antibiotic treatment, duration of hospital stay, VAS scores, quality of life (QOL, using for example 5D or 15D validated QOL questionnaire), length of sick leave and treatment costs.

2. Sample size calculation

The primary objective of the study is to demonstrate that p.o. antibiotic therapy is non-inferior compared to a combination of i.v. and p.o. antibiotic therapy, i.e. the trial is designed as a non-inferiority study and sample size calculations were based on non-inferiority test for binomial proportion. Sample size was calculated from an estimated success rate of 73% for

i.v. + p.o. antibiotic group during the one year follow-up based on the results of our previous APPAC trial[2]. The hypothetical difference between the two groups ((i.v. + p.o.) vs (p.o.)) was set to zero and non-inferiority margin was set to 6 percentage points. We estimated that a total of 469 patients would yield a power of 0.9 (1-β) to establish whether p.o. antibiotic therapy was non-inferior to i.v. + p.o. using a one-sided significance level (α) of 0.05. With an estimated dropout rate of 15% total of 552 patients, 276 patients per group will be enrolled in the study. Targeted minimum sample size per study hospital will be 20 patients.

3. Interim analysis

When 250 patients have been enrolled to the study and discharged from the hospital, or even at an earlier stage if the investigators think it is necessary, the point estimate of the success rate at discharge will be calculated by study statistician and evaluated in each group to ensure patient safety. If the proportion is below 70% in at least one of the groups, the study will be terminated. No statistical tests will be conducted in interim analysis and therefore no corrections to the p-values are needed in the final analyses of the study.

4. Statistical analysis

Categorical variables of the study will be characterized using frequencies and percentages. For continuous variables means and standard deviations, or medians with range and 25^{th} and 75^{th} percentiles will be used. The study site differences will be evaluated in statistical models and if major differences are detected, more complicated statistical models will be used in the analyses of primary and secondary outcomes. P-values less than 0.05 will be considered statistically significant. The analyses will be based on the intention-to-treat (ITT) principle (all randomized excluding possible erroneously randomized patients with a primary CT diagnosis of complicated appendicitis). Statistical analyses will be performed using SAS System for Windows, Version 9.4 or later (SAS Institute Inc., Cary, NC).

4.1 Primary outcome

The primary objective of the study is to demonstrate that p.o. antibiotic therapy is as efficient and safe as i.v. + p.o. antibiotics for CT-scan confirmed uncomplicated acute appendicitis. The primary outcome will be evaluated in two stages using the following statistical hypotheses:

1) H_0: $p_1 \leq 65$ and $p_2 \leq 65$

H_1: $p_1 > 65$ and $p_2 > 65$

2) H_0: $p_1 - p_2 > 6$

H_1: $p_1 - p_2 \leq 6$

where p_1 is success of treatment proportion in i.v. + p.o. group and p_2 for p.o. group and $p_1 - p_2$ is the difference between the groups ((i.v. + p.o.) – po).

The point estimate with 95% confidence interval (CI) for success of treatment will be calculated for both groups and if lower limit of 95% CI ≥ 65%, then treatment is good enough. Non-inferiority of p.o. antibiotics vs. i.v. + p.o. antibiotics will be evaluated using a two-sided 90% CI of proportion difference between groups and one-sided Wald test for non-inferiority with an α level of 0.05. Non-inferiority margin for difference is 6 percentage points. In cases of patients lost to follow-up, for the primary end-point of treatment success and the secondary endpoints of late recurrence, morbidity, and mortality, missing data will be retrieved from hospital registries.

Regarding the primary outcome, multiple prognostic factors potentially effecting the primary outcome will also be analyzed; for example patient age, gender, body mass index, laboratory test values, fever, VAS score, symptoms, and symptom duration prior to hospitalization as well as imaging features such as appendiceal diameter, minor fluid or edema around the appendix.

4.2 Secondary outcomes

The secondary outcomes will be analyzed using chi-squared test, independent samples t-test or Mann-Whitney U-test. The assumptions of tests will be checked for justification of the analyses. For the secondary outcomes two-sided p-values will be used. The subjects with missing data will automatically be excluded from the analyses of the variables in concern.

The secondary outcomes will be evaluated primarily at the predefined follow-up time points, excluding the comprehensive QOL life assessment, which will mainly be carried out at the 3 year time point, considering the current understanding that most of the recurrences after antibiotic treatment will occur during the first 2 years after initial treatment.[3] In a small subset of patients, earlier QOL data will be retrieved to assess the potential differences.

4.3 Subgroup analyses

Additional analyses will be performed for overall morbidity using intention-to-treat principle.

5. Follow-up

The primary outcome results of the trial will be assessed after one-year-follow-up of the patients. The patients will be assessed for the secondary outcomes also at 3, 5 and 10 years after treatment and the data is evaluated in every time-point. If the primary endpoint analysis at 1 year shows non-inferiority of the p.o. antibiotic therapy, this primary endpoint will also be assessed at further follow-up time points.

1. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250(2):187-196.
2. Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA.* 2015;313(23):2340-2348.
3. Salminen P, Tuominen R, Paajanen H, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. *JAMA.* 2018;320(12):1259-1265.