STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN, original date 6.9.2012

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The treatment of periappendicular abscess after the acute phase: laparoscopic interval appendectomy vs. follow up with MRI imaging (PeriAPPAC trial)

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1. Background

Acute appendicitis is the most common reason for emergency surgery with over 300.000 annual appendectomies in the United States[1]. In 2007 there were a total of approximately 5000 appendectomies performed for acute appendicitis in Finland[2]. In some patients with complicated acute appendicitis, the inflammation progresses quickly to perforation and generalized peritonitis. In other patients with appendiceal perforation, the perforation is enclosed resulting in the formation of a periappendicular abscess. Out of all patients with acute appendicitis, 3 to 10 % present with a periappendicular abscess[3 4]. The risk of perforation has been shown to increase if the duration of the symptoms exceeds 36 hours or if the appendiceal lumen is blocked by an appendicolith[5 6]. The traditional management of periappendicular abscess is non-operative treatment with antibiotics followed by a prophylactic interval appendectomy.

1.1 Diagnosis of periappendicular abscess

Suspicion of a periappendicular abscess arises, when typical symptoms of appendicitis have lasted over three days. Fever, significantly elevated CRP levels and a lower right quadrant abdominal pain are typical symptoms, but finding a palpable mass is challenging, especially in obese patients. Symptoms and findings can be atypical and in those occasions, the diagnosis may be defined at operation, if no preoperative imaging studies have been performed. The development of imaging modalities have markedly improved the diagnosis of periappendicular abscess. Computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound have all enabled rapid diagnosis.

1.2 Treatment of periappendicular abscess

Acute surgical treatment of periappendicular abscess can be technically challenging due to inflamed tissues and altered anatomy and the closure of the appendiceal stump may be challenging. In the acute phase, periappendicular abscess might even simulate a tumor and lead to unnecessary ileocecal resection or even right sided hemicolectomy. Acute surgical treatment of periappendicular abscess is associated with a threefold increase in complication risk when compared to initial conservative treatment[3 7].

Due to the increased risk of complications, the standard treatment of a periappendicular abscess has been antibiotic therapy combined with drainage, if necessary. An interval appendectomy has often been scheduled to avoid possible recurrent appendicitis. The need for an elective interval appendectomy has been questioned based on the associated morbidity and reported low recurrence rates. Reported recurrence rates vary between 7-14%, but after the first year, the risk decreases to 2%[3 8]. Recurrence may be predicted in patients with a CT – confirmed appendicolith and these patients can be treated with interval appendectomy. When taking into consideration the reported complication rates of elective interval appendectomy (11-18%)[3 9], a routine interval appendectomy may not be necessary for all patients. Elective interval appendectomy has also been advocated in order not to miss a possible neoplasm. However, this neoplasm rate is reported to be only 2 % and the majority of neoplasms are found in patients over 40 years of age. To exclude a neoplasm, patients should however undergo imaging with MRI or CT as well as colonoscopy[3 7].

1.3 Significance of the study

This prospective, randomized PeriAPPAC study was initially intended to be performed in concurrence with the APPAC-study comparing the conservative treatment of appendicitis

(antibiotics) with operative treatment (appendectomy). However, the recruitment of APPAC study patients was already completed in June 2012 prior to initiation of the PeriAPPAC trial and the patients will be recruited in PeriAPPAC without concurrently ongoing APPAC study. PeriAPPAC study has notable significance, as if the study hypothesis is confirmed, a significant part of routine interval appendectomies could be abandoned in the future. This would avoid morbidity associated to surgical treatment as well as reduce health care costs. Results would be significant as to our knowledge there is only one previous randomized study with small study population (n=20) assessing the need for interval appendectomy after initial conservative treatment of periappendicular abscess[10].

2. Study aims and endpoints

The purpose of this randomized prospective study is to compare interval appendectomy to follow-up with MRI-imaging in patients with initially successfully managed periappendicular abscess. The primary endpoint is the treatment success evaluated at one year after the intervention. In the interval appendectomy group treatment success was defined as both successful appendectomy and non-complicated recovery (overall postoperative morbidity) and in the follow-up group as absence of recurrent acute appendicitis during follow-up period. The predefined secondary endpoints included possible appendiceal or colonic tumors, possible inflammatory bowel disease diagnosis (ulcerative colitis or Crohn's disease), the length of hospital stay and sick leave, and treatment costs.

3. Study hypothesis

Interval appendectomy may not be necessary for all patients after initial successful treatment of periappendicular abscess due to low recurrence rate, i.e. avoiding unnecessary appendectomies.

4. Patients and methods

All patients with a periappendicular abscess will be evaluated for study enrollment. Main research hospital is Turku University Hospital and other research hospitals are APPAC research hospitals Oulu University Hospital, Tampere University Hospital, Kuopio University Hospital and Seinäjoki Central Hospital. The recruitment goal for each treatment arm according to initial power analysis is a minimum of 55-100 patients to form a minimum size of 110 patients in the whole study population.

4.1 Inclusion criteria

- Age 18 to 60 years
- CT- or MRI-confirmed periappendicular abscess after initial successful conservative treatment with antibiotics and/or drainage, if necessary.

4.2 Exclusion criteria

- Suspicion of a neoplasm at CT- or MRI-imaging
- Age under 18 years or over 60 years
- Pregnancy or lactating
- Allergy to contrast medium or iodine
- Renal insufficiency, elevated creatinine level
- Diabetes mellitus with metformin medication

- Unsuccessful initial conservative treatment of periappendicular abscess (i.e. appendectomy or other bowel resection including the appendix)
- Lack of co-operation (unable to give informed consent)
- Severe systemic illness
- Previous non-operative management of acute appendicitis

4.3 The PeriAPPAC study flow

All patients presenting at the surgical emergency department with a suspected periappendicular abscess will undergo laboratory tests (CBC, CRP, electrolytes, urine analysis, pregnancy test for the female patients) and they undergo CT-imaging after the laboratory tests are available. A MRI diagnosis is also accepted for study inclusion, but ultrasound-diagnosis is not sufficient for study enrollment. During work hours, the image is interpreted by consultant radiologist or resident radiologist. During on call hours, the image is interpreted by on call radiologist. The CT scan is made according to APPAC protocol and in the report is given with preapproved criteria.

If the CT diagnosis is periappendicular abscess and the patient doesn't have symptoms of peritonitis, the patient is started with i.v fluids and antibiotics and admitted to surgical ward. Antibiotics are continued as long as patients' clinical state allows discharge. If deemed necessary, the abscess may be radiologically drained. If the clinical condition deteriorates and there is suspicion of peritonitis, an emergency appendectomy is performed according to normal treatment protocol. At discharge, per oral antibiotics are continued for a week according to normal treatment protocol.

Randomization

At the time of patient discharge, i.e. after successful initial non-operative management, the research surgeon informs the patient of the study and written informed consent is obtained. After consent, the patient is randomized using sealed opaque envelope method to either the follow-up with MRI imaging treatment arm or the interval appendectomy treatment arm. Research surgeon fills out the initial research form, which is kept in locked filing cabinet. Patient is given approximately a week of sick leave and advised to contact in case of recurrent symptoms.

4.4 Follow up with MRI

A colonoscopy and a MRI are performed at three months from initial discharge to exclude neoplasies. If a suspicion of a malignancy arises, patients are treated according to standard principles of surgical oncology.

If a patient in follow up treatment arm presents with suspected recurrent appendicitis, they are managed with standard preferably laparoscopic appendectomy and the removed appendix will undergo standard histopathological assessment. If a patient presents with recurrent abscess, the acute phase is treated as necessary to clinical condition and followed by an interval appendectomy.

4.5 Interval appendectomy

A colonoscopy is performed at three months preceding the interval appendectomy. Laparoscopic approach is used at all times if possible. The removed appendix will undergo standard histopathological assessment.

The post-operative protocol is managed as usual and the patient will be discharged based on when clinical condition, usually either 1st or 2nd post-operative day. A research form is filled at discharge, which is kept in a locked filing cabinet. Sick leave is written as needed, usually 1-3 weeks. Suture removal is advised in primary healthcare, and pain medication prescription is written as needed.

4.6 Study Follow-up

Follow-up is organized and followed by the research surgeons of the each participating hospital. The patients are contacted at two months and one year. Long-term follow up is done with either patient interviewing form via postal service or with telephone questionnaire at 3, 5 and 10 years.

5. Statistical analysis and reporting of results

The sample size calculation for the trial is based on the primary outcome assuming that all patients randomized to surgical group would undergo a successful interval appendectomy. For computational reasons, the success rate for surgery is assumed to be 99%. The findings of prior studies indicate recurrence rates of acute appendicitis of 5-20% for follow-up resulting in anticipated success rate of approximately 85% in the follow-up group. Because the non-inferiority is evaluated using the lower limit of 95% confidence interval of treatment efficacy, we use 75% success rate in follow-up group as marginal value, and a 24% (99%-75%) non-inferiority margin is used in the sample size calculations. We estimate that a total of 110 patients (55 patients per group) would yield a power of 0.9 (1-β) to establish whether follow-up group is not inferior to surgery using a significance level α of 0.05. With approximately 10% drop-out rate our aim is to enrol 122 patients.

6. Ethical considerations

The purpose of the study is to compare interval appendectomy to follow-up with MRI in patients with initially successfully conservatively managed periappendicular abscess. Interval appendectomy is a common treatment strategy, even though the need of a subsequent interval appendectomy has been questioned in a few retrospective studies. No large prospective, randomized trials have been reported. If study hypothesis is confirmed, patients would avoid unnecessary surgical treatment decreasing the associated morbidity and resulting in cost savings.

To accurately diagnose patients with periappendicular abscess, a CT or a MRI needs to be used. To avoid unnecessary radiation, children and pregnant women are excluded from the study, as well as patients with allergies or renal insufficiency.

The primary conservative treatment of periappendicular abscess with antibiotics is current clinical practise and based on the clinical condition of the patient; if there are no signs of peritonitis, the treatment is initially non-operative. Non-operative treatment is safe to patients as adequate follow up is available and a change in treatment protocol is available, if clinical condition changes.

To reduce the risk of missing a diagnosis of a malignant disease (cecal neoplasm), all research patients in both treatment arms are performed a colonoscopy. Interval appendectomy patients have available histopathology of the removed appendix and the follow-up group patients undergo a MRI.

7. Research group

The study primary investigator is docent Paulina Salminen from Turku University Hospital and the other researcher from the main research center is docent Juha Grönroos. Other researchers are Tero Rautio MD, PhD and Jari Mällinen, MD from Oulu University Hospital; Pia Nordström MD, PhD from Tampere University Hospital; Heini Savolainen, MD, PhD from Kuopio University Hospital; Tuomo Rantanen, MD, PhD from Seinäjoki Central Hospital. Study statisticians are Saija Hurme, MSc and Pasi Ohtonen, MSc. All members of research team participate in the reporting of results.

8. References

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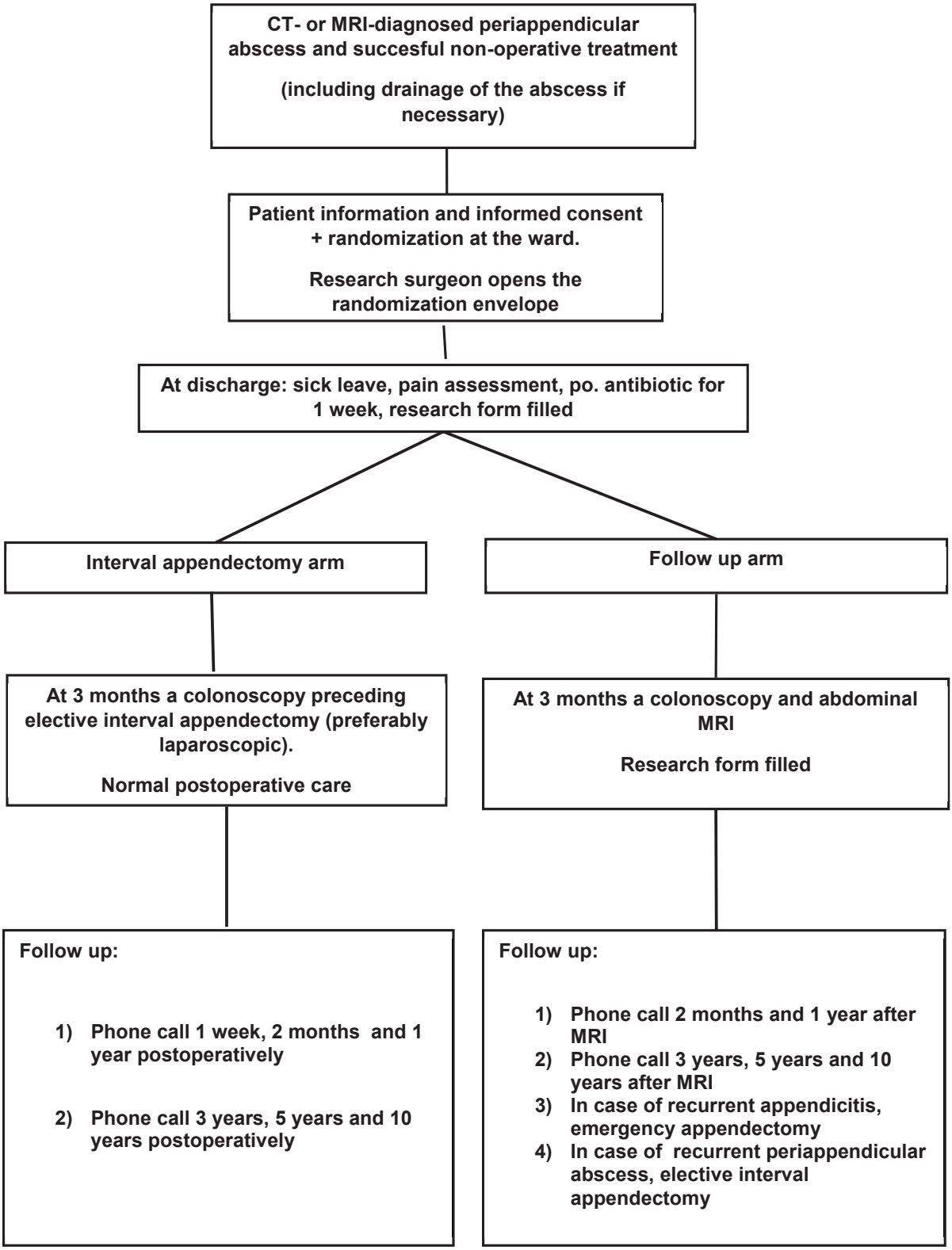
Patient flow chart of PeriAPPAC study.



5.10.2012 Saija Hurme

PeriAPPAC -study, sample size calculations

The study wants to show that the treatment success is not significantly inferior in the follow up group to that of the treatment success in the operative intervention group.

Zero hypothesis and alternate hypothesis:

H_0: The treatment success in the follow up group is significantly inferior to that of in the operative intervention group (the definition of significantly inferior is set to be 25-30 percentages inferior treatment success).

H_1: The treatment success in the follow up group is not significantly inferior to that of in the operative intervention group.

- Alpha limit is set as 0.05 (the limit of significant p-value used) and the test power value (1-β) is set as 0.9
- The assumption is made that operative treatment success is very close to 100%. To take into account that in some patient operative treatment could fail, in calculations 99% is used (treatment success in operative intervention group)
- The assumption is made that in the follow up group the treatment success is 85% (treatment success in the follow up group).
- The follow up groups success rate and operative intervention groups success rate is allowed to differ 24% or 29% (margins), thus the lower limit of follow up groups treatment success rate is set between 75 or 70% (lower limit).
- Total sample size is set 110-138 which sets 55-69 per treatment group. Drop out estimate considered, n=122.

		Treatment success					
Alpha	1-beta (power)	Oper	Follow	Margin	Lower	n/group	N
0.05	0.9	99	85	-24	75	**55**	**110**
0.05	0.9	99	80	-29	70	**69**	**138**