The CHildren's INterval Appendicectomy (CHINA) Study

A Prospective Randomised Evaluation of Interval Appendicectomy versus Conservative Follow-Up Following Successful Non-Operative Treatment of Appendix Mass in Children

STUDY PROTOCOL
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1. Introduction

Up to 22% of children with acute appendicitis present with a walled-off mass surrounding the inflamed appendix known as an appendix mass (AM). Patients presenting with AM are usually treated non-operatively with broad spectrum intravenous antibiotics as the risk of complications from operative intervention in the presence of an inflammatory mass is high.[1] Traditional surgical teaching states that interval appendicectomy (IA) should be performed following successful non-operative treatment in order to avoid future recurrence of acute appendicitis. However this approach has recently been questioned in both the paediatric[2] and adult literature.[3]

Proponents of IA argue that the risk of recurrent appendicitis is high and that interval appendicectomy is safe, carries minimal complications and has a low morbidity. Those who argue that IA is unnecessary cite the opposite: a low incidence of recurrent appendicitis and avoidable morbidity, hospital stay and cost associated with IA. Additionally there may be a small risk of missing an underlying diagnosis in patients who do not have an IA. Whilst the risk of recurrent appendicitis is difficult to directly compare with the complications and morbidity of interval appendicectomy, accurate reliable data relating to these two methods of management would allow clinicians, patients and parents to make an evidence-based decision. Such data are not currently available.

2. Aim of the study

The principle research question that we aim to address is whether interval appendicectomy is justified following successful non-operative treatment of appendix mass in children.

The main factors that contribute to answering this question are:
1. the true incidence of recurrence of acute appendicitis following successful conservative treatment of appendix mass
2. the morbidity and risks associated with interval appendicectomy
3. the risk of missing an alternative diagnosis by not performing an interval appendicectomy
4. the cost effectiveness of each method of treatment

We hypothesise that the risk of recurrent acute appendicitis is low and that therefore routine interval appendicectomy is unnecessary.

This research aims to generate reliable, accurate data relating to these factors from a prospective randomised study. Only once such data exist can clinicians, patients, parents and policy makers truly assess whether interval appendicectomy is necessary and cost effective.

3. Scientific background

Risk of recurrent appendicitis
The actual risk of recurrent acute appendicitis in children is largely unknown due to a lack of quality data. No prospective studies comparing IA with continued conservative management – a watch-and-wait approach - exist. In the largest cohort study of paediatric patients available. Puapong et al[4] described a recurrence rate of 8% in 61 children. The time to recurrence was <6 months in 80% of cases. Their data was

based on a retrospective analysis of hospital discharge data and as such subject to inherent biases.

We have recently performed a systematic review of the literature regarding the incidence of recurrent appendicitis following successful non-operative treatment of AM in children (Oral presentation BAPS 2010). There were no prospective studies comparing routine IA with routine non-operative management. Four studies met the inclusion criteria. However one study included patients later reported in a report from the same institution and was therefore excluded. Three studies were therefore included, relating to 127 patients. All studies were retrospective reviews and none reported a comparison group of children who underwent IA. Overall the risk of recurrence of appendicitis was 20.5% (95%CI 14.3-28.4). Time to recurrence was <6 months in over 80% of cases. However none of these studies include a comparison group of children who underwent planned IA and all were retrospective resulting in the potential for significant bias in the results.

If these data are correct, to submit all children to IA would mean operating on approximately 80% of children unnecessarily.

In the absence of quality paediatric data, we have also examined the adult literature. Similar debate exists with regard to the need for IA in adult patients. A recent meta-analysis[12] suggests that the risk of recurrent acute appendicitis is 7.4% (95%CI 3.7 – 11.1%). There has been one small scale randomised controlled trial comparing treatments for AM.[13] In this 3 arm study patients with AM were all initially managed non-surgically followed by either delayed appendicectomy (following resolution of the mass during the same admission), interval appendicectomy (6 weeks later) or no appendicectomy. The recurrence rate of acute appendicitis in the group managed completely non-operatively was 10%. These patients all underwent uncomplicated appendicectomy. Despite there being no complications related to IA, the authors concluded that a completely non-operative approach was preferable due to a low risk of recurrent appendicitis, a shorter hospital stay and a more rapid return to work.

Morbidity of interval appendicectomy
IA has been proposed as a reliable means of preventing acute appendicitis again in the future. However, it requires a hospital admission (usually 2-3 days), time away from school or other daily activities, incurs a cost and places the patient at risk of operative complications. Whilst generally considered to be a safe and effective procedure which may be performed laparoscopically, the risk of complications following interval appendicectomy is not negligible and has been reported to be as high as 17% in children.[14] Our systematic review of the literature suggests that the incidence of complications following interval appendicectomy is 3.4% (95%CI 2.2-5.1). Furthermore interval appendicectomy requires a hospital admission of 2-3 days.

Risk of missing alternative diagnosis
If an interval appendicectomy is not performed there remains a risk of missing an undiagnosed condition present in the appendix. The most common condition in childhood is that of a carcinoid tumour. According to our systematic review the prevalence of carcinoid tumour at interval appendicectomy is 0.9% (95%CI 0.5-1.8).

4. Research plan and methods

We plan a prospective multicentre randomised evaluation involving Paediatric Surgery units in the United Kingdom. Children (<16yrs) who presented with acute

appendicitis with an appendix mass and have undergone successful non-operative treatment (i.e. without appendicectomy) will be eligible for inclusion

Specifically, to be included in the study, the patient must satisfy each of the following criteria:

1. diagnosis of acute appendicitis with appendix mass;
2. appendix mass palpable clinically, during examination under anaesthetic or identified radiologically (ultrasound or CT)
3. have been successfully treated non-operatively during the acute stage of the illness

Note: no formal definition of an appendix mass is necessary other than a mass which in the opinion of the Consultant in charge of the child's care warrants non-operative rather than operative treatment.

Patients with any of the following criteria will be excluded:

1. age less than 3 years at the time of initial presentation;
2. co-existing gastrointestinal disease e.g. inflammatory bowel disease;
3. presence of significant co-existing medical conditions or immune defect

Children fulfilling the inclusion criteria, after parental (and patient if applicable) informed consent, will receive either:

1. planned interval appendicectomy following discharge (interval appendicectomy group)

   Note: interval appendicectomy may be performed open or laparoscopically at the discretion of the operating surgeon and at a time scale determined by operating surgeon's current practice

2. waiting policy with 3 monthly follow-up in surgical clinic for at least one year following discharge ('watchful waiting' group). The outcome of this group could be either (i) no recurrence of acute appendicitis (this should be confirmed at the clinic appointments) or (ii) acute appendicitis requiring appendicectomy with histopathological evidence of acute inflammation at the time of appendicectomy or (iii) acute appendicitis with recurrent appendix mass (such patients will not be eligible for re-entry into the study and should be offered interval appendicectomy) or (iv) persistent abdominal symptoms which in the view of the treating clinician warrant interval appendicectomy.

Allocation to groups (1:1 ratio) will be made by weighted minimisation at enrolment into the study using the following criteria:

1. gender ([male], [female])
2. presence of faecolith on radiological investigation ([yes], [no])
3. age ([3-9yrs], [10-15yrs])
4. collaborating centre

Minimisation and randomisation will be performed using a purpose built randomisation software package designed specifically for randomised prospective studies. It is envisaged that this process will be performed by the participating centre over the internet.

The primary outcome measures of this study will be:

1. Watchful waiting group: the number of patients developing recurrent acute appendicitis within 1 year of discharge following successful non-operative treatment of appendix mass (diagnosis confirmed by evidence of acute inflammation in resected appendix or clinical diagnosis of recurrent appendix mass in the opinion of the Consultant responsible for the patient's care).

2. Interval appendicectomy group: the incidence of significant complications during or following interval appendicectomy. Significant complications are defined as any complication requiring additional or unanticipated treatment and include intestinal perforation, haemorrhage requiring transfusion, wound infection, abscess formation, post-operative small bowel obstruction, prolonged ileus (>72hrs post-operatively). Conversion of a laparoscopic to open interval appendicectomy for a technically difficult procedure in the absence of other complications shall not be regarded as a significant complication.

Additional data to be collected includes:

Interval appendicectomy group
1. duration of hospital admission for interval appendicectomy
2. cost of treatment (full economic analysis)
3. days off school / normal daily activities following interval appendicectomy
4. histopathological assessment of resected appendix

Watchful waiting group
1. duration of hospital admission for recurrence
2. outcome of recurrence including all complications
3. days off school / normal daily activities relating to recurrence
4. cost of treatment of recurrence (full economic analysis)
5. episodes of otherwise unexplained abdominal pain during the first year following discharge and time off school / normal daily activities relating to these (assessed at clinic appointment)

Parents/Patients who do not consent for the study
Parents/Patients who do not consent for the study will be asked for permission to collect data on their child for the purposes of establishing a dataset of children who are eligible but not enrolled. Such data will be anonymised and handled in an identical way to the data relating to patients in the study. An identical dataset to that being collected from individuals in the study will be collected but the course of treatment for these children will be determined by their treating clinician rather than by randomisation. Written consent will be obtained from the parents of such children. If parents do not consent to such data collection then a minimal dataset will be recorded consisting solely of demographic data. It is important to collect such data to validate the applicability of any findings of the study.

5. Sample size calculation

We have based this calculation on an assumption of a 20% risk of recurrent acute appendicitis within the first year in the wait-and-see group and a zero incidence of recurrence on the interval appendicectomy group. In order to detect a statistically significant difference in the incidence of recurrent acute appendicitis in the wait-and-see group compared with the interval appendicectomy group will require 40 patients

per group at 90% power (a=0.05). However, in order to provide as strong evidence as possible on the natural history of this condition we will aim to recruit 50 patients per group.

6. Data collection and statistical analysis

A designated administrator at every collaborating centre will obtain data that will be forwarded to the study coordinators. Data will be entered into a specifically designed database and analysed on an intention-to-treat basis.

Primary outcome measures will be reported quantitatively as it is not clinically appropriate to compare a recurrence rate with complications of a procedure. Moreover the reporting of these data will allow for an evidence based decision to be taken in the management of these patients in the future.

Other outcome variables will be analysed with multivariate binary regression analysis, ordinal regression analysis, Mann-Whitney U test, and χ^2 tests, as appropriate. All statistical analyses will be calculated with adjustment for all minimisation criteria. Skewed continuous data will be transformed to resemble a normal distribution before analysis. Statistical analysis will be performed by one of the research team who has experience in statistical analysis of prospective randomised studies of this nature.

Stopping rules
In order to ensure that equipoise is maintained throughout the duration of the study, an interim analysis will be performed after data are available for the first half of the recruited patients. Stopping rules will be established prior to study initiation based on the incidence of recurrent appendicitis in the watchful waiting group. The interim analysis will be performed by a statistician with experience in the statistical analysis of randomised studies and not involved in the clinical management of subjects in the study.

7. Organisation and monitoring

The study will be co-ordinated by a Research Fellow based at Southampton University Hospitals NHS Trust. In order to maximise the compliance of participating centres in the study, a link surgeon will be identified at each centre who will liaise with the trial co-ordinating centre.

Confidentiality of data will be ensured. To ensure that the study progress is in accordance with Medical Research Council (U.K.) guidelines for good clinical practice in multicentre studies, a Study Steering Committee will be established. This will include a limited number of members including:

a) independent Chairman (not involved in Study);
b) independent members (Paediatric Surgeon and Paediatrician);
c) study co-ordinator;
d) principal investigator or nominated deputy

The role of the steering Committee is to provide overall supervision of the study and ensure that the study is conducted to rigorous scientific, clinical and ethical standards. It will particularly concentrate on progress of the study, adherence to the

protocol, data collection and maximise the chances of completion within the agreed timetable. This committee will meet 6 monthly or more frequently if required.

8. Feasibility and timetable

One hundred children are required to fulfil the sample size requirements for this study. On average each Paediatric Surgical Unit in the UK will see 5-10 cases of appendix mass each year. The involvement of 10 centres in this study would therefore see recruitment to the study completed in 2 years with a further year for follow-up to be completed.

This project will be co-ordinated by a co-ordinator at the lead centre. A nominated investigator will be identified at each collaborating centre who will be responsible for the implementation of the study locally. The co-ordinator will liaise with the nominated investigator at each centre to ensure compliance with the research protocol, provide assistance where possible and ensure all data are collected.

The research team has been selected for its clinical and research experience, particularly in the design and running of randomised controlled studies in the field of Paediatric Surgery.

9. Relevance and Publication Policy

It is anticipated that the proposed project will provide quality evidence on which clinicians, parents and patients can base the decision of whether IA is justified following successful non-operative treatment of an appendix mass. Data from this study will we submitted for presentation at local, national and international meetings and submitted for publication in international peer reviewed journals. Authorship of any such presentations and publications will be in accordance with the requirements of the International Committee of Medical Journal Editors (ICMJE) and as follows:

Authorship of any presentation or publication will be limited to the principle investigator and those named as co-investigators at the top of this document. The nominated investigator at each collaborating centre will be acknowledged in the manuscript under the heading ‘Acknowledgements’ as having contributed to the study. The National Library of Medicine now lists and indexes both the study group and the individuals acknowledged such that the nominated investigator at each collaborating centre will be identified as having contributed to this study. The nominated investigators contribution to the study will thus be recognisable.

Results of the study will be made available to those participants or their parents who specifically request it.

10. Financial implications

Unfortunately it will not be possible to offer any financial incentive for institutions who agree to collaborate in this study. However, it is anticipated that the recruitment of patients into this study should not result in any significant costs to institutions involved. Whilst it is likely that the additional out-patient reviews in the ‘watchful waiting’ group will result in a small additional costs to each institution, there may be cost savings in the ‘interval appendicectomy’ group as a fewer number of children will undergo interval appendicectomy than is current practice in many centres. We

therefore anticipate that, at worst, the involvement of any centre in this study will be 'cost neutral'.

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