Active observation versus interval appendicectomy after successful non-operative treatment of an appendix mass in children (CHINA study): an open-label, randomised controlled trial

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Summary

Background Despite a scarcity of supporting evidence, most surgeons recommend routine interval appendicectomy after successful non-operative treatment of an appendix mass in children. We aimed to compare routine interval appendicectomy with active observation.

Methods We enrolled participants in the CHildren's INterval Appendicectomy (CHINA) study, a multicentre, open-label, randomised controlled study at 19 specialist paediatric surgery centres, 17 of which were in the UK, one in Sweden, and one in New Zealand. 106 children aged 3–15 years were assigned (1:1) by weighted minimisation to interval appendicectomy or active observation with minimisation for age, trial centre, sex, and presence of a faecolith on imaging. Eligible children had acute appendicitis with an appendix mass and were successfully treated without appendicectomy or other surgical intervention. Children were excluded from the study if they had coexisting gastrointestinal disease or had a substantial coexisting medical condition or immune defect. Because of the nature of the interventions, blinding was not possible. The primary outcome was the proportion of children developing histologically proven recurrent acute appendicitis or a clinical diagnosis of recurrent appendix mass within 1 year of enrolment after successful non-operative treatment of appendix mass (active observation group) and incidence of severe complications related to interval appendicectomy. Data were analysed on an intention-to-treat basis. This study is registered with ISRCTN, number 93815412.

Findings Between Aug 8, 2011, and Dec 31, 2014, we randomly assigned 106 patients, 52 patients to interval appendicectomy and 54 to active observation. Two children in the interval appendicectomy group were withdrawn due to withdrawal of consent; two in the active observation group were withdrawn because they became ineligible after allocation. Six children under active observation had histologically proven recurrent acute appendicitis. Three children in the interval appendicectomy group had severe complications. Thus, the proportion of children with histologically proven recurrent acute appendicitis under active observation was 12% (95% CI 5–23) and the proportion of children with severe complications related to interval appendicectomy was 6% (95% CI 1–17).

Interpretation More than three-quarters of children could avoid appendicectomy during early follow-up after successful non-operative treatment of an appendix mass. Although the risk of complications after interval appendicectomy is low, complications can be severe. Adoption of a wait-and-see approach, reserving appendicectomy for those who develop recurrence or recurrent symptoms, results in fewer days in hospital, fewer days away from normal daily activity, and is cheaper than routine interval appendicectomy. These high-quality data will allow clinicians, parents, and children to make an evidence-based decision regarding the justification for interval appendicectomy.

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See Online for appendix

Introduction

Acute appendicitis is the most common general surgical emergency in children. The lifetime risk of the development of appendicitis is 7–8% with a peak incidence in the second decade of life.[1] Approximately 9% of children with acute appendicitis present with a palpable, fixed, walled-off mass surrounding the inflamed appendix known as an appendix mass.[2] Treatment of the acute phase of appendix mass in children is usually non-operative with broad-spectrum intravenous antibiotics because the risk of complications from attempted appendicectomy in the presence of an inflammatory mass is high.[3] After successful non-operative treatment, present surgical dogma is that interval appendicectomy should be done to avoid future recurrence of acute appendicitis. However, this approach has been questioned in both the paediatric[4] and adult[5] published literature.

When considering whether to do an interval appendicectomy or not in this clinical scenario, clinicians and parents must balance risks and benefits related to each management option. The main factors that contribute to the decision-making process related to interval appendicectomy are: the incidence of recurrent acute appendicitis after successful conservative treatment of

Research in context

Evidence before this study

Most paediatric surgeons treat children who present acutely with an appendix mass non-operatively. Additionally, more than two-thirds of surgeons routinely recommend interval appendicectomy, yet the justification for interval appendicectomy has never been prospectively challenged. A systematic review of retrospective studies suggested the incidence of recurrent appendicitis was approximately 20% and the incidence of complications from interval appendicectomy was 3%.

Added value of this study

This study has provided prospectively collected, high-quality data with which clinicians, parents, and children can, for the first time to our knowledge, make an evidence-based decision regarding the justification for interval appendicectomy. Within a year of randomisation, the incidence of histologically proven recurrent appendicitis in children randomly allocated to active observation was 12%, and more than 75% of children avoided appendicectomy. Severe complications related to interval appendicectomy occurred in 6% of patients.

Implications of all the available evidence

More than three-quarters of children can avoid appendicectomy during early follow-up after successful non-operative treatment of an appendix mass. Although the risk of complications after interval appendicectomy is low, complications can be severe. Adoption of a wait-and-see approach, reserving appendicectomy for those who develop recurrence or recurrent symptoms, results in fewer days in hospital and days away from normal daily activity, and is cheaper than routine interval appendicectomy.

an appendix mass, the morbidity and risks associated with interval appendicectomy, the risk of missing an alternative diagnosis (such as a carcinoid tumour) by not doing an interval appendicectomy, and the cost-effectiveness of each method of treatment. Proponents of interval appendicectomy argue that the risk of recurrent appendicitis is high and that interval appendicectomy is safe and has low morbidity. Those who opt for conservative management cite the opposite: a fairly low incidence of recurrent appendicitis and avoidable morbidity, hospital stay, and cost associated with interval appendicectomy. A survey[6] of UK-based paediatric surgeons in 2009 reported that 68% routinely recommend interval appendicectomy for all children after successful conservative management of appendix mass.

For the **protocol** see http://www.uhs.nhs.uk/Media/Southampton-Clinical-Research/Research-protocol/CHINA-Protocol-v2-4.1.11.pdf

A systematic review published in 2011[7] estimated the risk of the development of recurrent acute appendicitis after successful non-operative treatment of an appendix mass in children as 20%, and the incidence of complications after interval appendicectomy as 3%. A key finding of this review was the small number of published studies, most of which were retrospective and of fairly poor methodological quality. Only three studies contributed data to the outcome of recurrent appendicitis,[8–10] one of which suggested that the incidence of recurrent appendicitis was higher in children with a faecolith than children without a faecolith.[9]

To establish whether interval appendicectomy is justified, we designed the CHildren's INterval Appendicectomy (CHINA) study. This prospective, multicentre, open-label, randomised study aimed to generate high-quality prospective data to allow clinicians, parents, and patients to make an informed decision about the need for, and cost-effectiveness of, interval appendicectomy after successful non-operative treatment of an appendix mass in children.

Methods

Study design

We did a prospective, multicentre, open-label, randomised study in which children who had an appendix mass successfully treated non-operatively, were allocated by weighted minimisation to either routine interval appendicectomy or 1 year of active observation. We recruited participants from 21 specialist paediatric surgery centres. 19 of these centres were in the UK, one in Sweden, and one in New Zealand. Multicentre ethical approval was granted by the UK National Research Ethics Service (Ref: 10/H0501/67) in February, 2011. Local ethical approval was obtained in all non-UK centres before recruitment. The study was done according to one protocol.

Participants

Children (<16 years) who presented with acute appendicitis and an appendix mass were eligible for inclusion if they: had a diagnosis of acute appendicitis with appendix mass; had an appendix mass palpable clinically, during examination under anaesthesia or identified radiologically (ultrasound or CT); and had been successfully treated non-operatively during the acute stage of the illness and discharged home. Children were excluded from the study if they were younger than 3 years at the time of initial presentation, had coexisting gastrointestinal disease (eg, inflammatory bowel disease), or had a substantial coexisting medical condition or immune defect. Children younger than 3 years were excluded due to the difficulty in making a reliable diagnosis of appendix mass in this age group.

No formal definition of an appendix mass was used, rather the diagnosis was made by the surgeon in charge of the child's care on the basis of: clinical examination, examination under anaesthesia, or imaging (ultrasound or CT scan, or both). Successful non-operative treatment was defined as the child being well enough to be discharged home on oral antibiotics, having not undergone surgery or attempted surgery to remove the

appendix nor received percutaneous drainage of any appendix-related abscess.

All participants were enrolled into the study after informed parental consent. The study was explained to the parents and child if appropriate (depending on age) with the help of a study information sheet. Separate, age-specific, information sheets were provided to children aged 8–11 years and those aged 12–15 years. Children 12 years or older were able to provide their own consent for participation if they wished, in addition to, or in place of, parental consent.

Randomisation and masking

Participants were allocated to groups (1:1) by weighted minimisation (randomisation weighting of four) at the time of enrolment into the study with the following criteria: sex (male or female), presence of faecolith on radiological investigation (yes or no), age (3–9 years or 10–15 years), and collaborating centre.

Minimisation was set up with an online computerised service provided by the University of Aberdeen (Aberdeen, UK). This system allowed for concealment of previously allocated patients from all site investigators before allocation by minimisation. The nature of the interventions meant that blinding was not possible. We included the collaborating centre as one of the minimisation criteria to account for differences that might have existed in treatment approach between centres. We did not include individual surgeon as a minimisation criterion because the actual number of participants expected to be operated on by each individual surgeon was very low (less than one patient per surgeon when every surgeon from each participating centre was considered). Thus, it is highly unlikely that treatment by any individual surgeon would influence study results.

Procedures

Children were allocated to one of two groups: interval appendicectomy or active observation. In the interval appendicectomy group, children were scheduled to undergo elective interval appendicectomy (open or laparoscopic) at a timescale determined by the operating surgeon's present practice, but with an advisory timescale of 2–3 months after randomisation. Children were reviewed in the outpatient clinic at approximately 6 weeks after interval appendicectomy and again at 1 year after randomisation.

In the active observation group, children were not scheduled for routine interval appendicectomy but were reviewed every 3 months in the outpatient clinic for 1 year after randomisation. Any child who developed recurrent appendicitis or who had symptoms that in the opinion of the treating clinician warranted surgery, underwent appendicectomy by either open or laparoscopic approach at the surgeon's discretion.

Outcomes

As a result of the different nature of the interventions in each treatment group, the primary outcomes for each group were different. All outcomes were defined a priori. The primary outcome in the interval appendicectomy group was the incidence of severe complications during or after interval appendicectomy. A severe complication was defined as any complication requiring additional or unanticipated treatment, including, but not limited to, intestinal perforation, haemorrhage requiring transfusion, wound infection requiring antibiotics, abscess formation, postoperative small bowel obstruction, and prolonged ileus (>72 h postoperatively). Conversion of a laparoscopic to open interval appendicectomy in the absence of another complication meeting the above definition was not defined as a severe complication.

The primary outcome in the active observation group was the proportion of children developing recurrent acute appendicitis within 1 year of enrolment after successful non-operative treatment of appendix mass. Recurrent acute appendicitis was defined as appendicitis confirmed by evidence of acute inflammation on histological examination of the resected appendix or a clinical diagnosis of recurrent appendix mass in the opinion of the consultant responsible for the child's care. The presence of acute inflammation was based on consultant histopathologist report at each individual institution.

Secondary outcomes were selected on their ability to inform the aims of the study and were relevant to one or both treatment groups including: adverse events, duration of hospital admission related to the appendix over the 1 year after enrolment, cost of treatment related to the appendix at 1 year follow-up, days off school or normal daily activities related to the appendix at 1 year follow up, details of all surgical procedures done, and histopathological evaluation of any resected appendicectomy specimen. Although participant safety and serious adverse events were monitored in this study, neither were included as formal study outcomes because this study compared two treatments that are routinely used and considered standard of care.

Data relating to all outcomes were recorded prospectively at the local centre and forwarded to the collaborating centre (Southampton Children's Hospital) at completion of the study. Data related to hospital admission were recorded during or immediately after the admission. To capture data related to admission to another hospital during the 1 year follow-up period, participants were specifically asked whether they had had a hospital attendance or admission for abdominal pain or suspected appendicitis at follow-up consultations. At discharge from hospital, parents were provided with a diary card and asked to document days on which their child was unable to attend school or undertake normal daily activities during the follow-up period either due to hospital admission, recovery after hospital admission, or unexplained abdominal pain. Total length of stay during the 1 year follow-up period was calculated for all planned and unplanned hospital admissions related to the appendix or abdominal pain at any hospital.

Costs were obtained from each participating institution's finance department for the cost of running the operating

theatre for 1 h (including staff costs) during 2015 and the cost of a 24 h period on the paediatric surgical ward during 2015. Costs from international centres were obtained in local currency and converted into sterling with the exchange rate on Dec 31, 2015 (1 Swedish krona=0·0822 British pound; 1 New Zealand dollar=0·4604 British pound). Costs related to hospital admission and time in the operating theatre were calculated by multiplying these unit costs by time spent in hospital and time spent in the operating theatre respectively. Hospital admission cost and theatre cost were added to give a total cost per patient during the 1 year follow-up period.

Statistical analysis

The study sample size was calculated to be able to show a statistically significant difference in the incidence of recurrent appendicitis between treatment groups based on a 20% risk of recurrent acute appendicitis within the first year in the active observation group and a zero incidence in the interval appendicectomy group at 90% power. The sample size was set at 50 children in each treatment group.

Data were entered into a custom designed database in Microsoft Access, exported into Microsoft Excel for handling, and then analysed with statistical packages. All data were analysed initially on an intention-to-treat basis. Because of some crossover between groups, a secondary analysis was done based on the treatment actually received.

Primary outcomes and other categorical data are reported as incidence with 95% CI. Continuous data are reported as median with IQR. Between-group comparisons were made with the Mann-Whitney *U* test for univariate analyses. Multiple linear regression analysis of $\log_{10}$ (hours +1) and $\log_{10}$ (cost +1) transformed data was done as data were right skewed, adjusting for age, sex, presence of faecolith, and centre. Kaplan-Meier analysis was used to calculate recurrence risk over time and the log-rank test was used to compare subgroups of children. Statistical analyses were done with SPSS (version 22) and Prism (version 6.0); p values of less than 0·05 was considered significant.

The study was overseen by a steering committee that met before recruitment of the first participant and regularly for the duration of the study, and comprised the study coordinator (non-voting), two independent paediatricians, and an independent paediatric surgeon. Data were provided and statistically analysed by SE (not involved in clinical care). The steering committee monitored recruitment to the trial and trial conduct, and reviewed any protocol violations. The steering committee mandated that an interim analysis be undertaken after half of the sample size had been recruited and followed up for 1 year. This interim analysis would calculate the rate of recurrent appendicitis and, if found to be over twice that anticipated (ie, more than 40%), the study would be terminated early. This interim analysis was done as planned and the stopping rule not met. The study is registered with ISRCTN, number 93815412.

Role of the funding source

The funder had no role in study design, recruitment, data collection, data analysis, data interpretation, or writing of the scientific report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were enrolled in the study between Aug 8, 2011, and Dec 31, 2014. The 1 year follow-up period for the final participant therefore ended on Dec 31, 2015. The baseline characteristics of the study groups are shown in table 1. The study was open to recruitment in 21 centres with children actually enrolled in the study from 19 of these; two centres in the UK did not enrol any patients because no patients from those centres gave consent. 183 children were screened and met the eligibility criteria in the recruiting centres during the study period (figure). Of these, 106 children or their parents, or both, agreed to participate and were allocated to either interval appendicectomy or active observation.

52 children were allocated to interval appendicectomy. Of these, two children were withdrawn from the study due to withdrawal of consent for continued participation. Of the remaining 50 children, three more declined interval appendicectomy but were followed up for 1 year, two developed recurrent appendicitis before their planned interval appendicectomy, and one did not receive interval appendicectomy within the 1 year follow-up period. Therefore, 44 children in the interval appendicectomy group underwent interval appendicectomy during the study period. All 50 children allocated to the interval appendicectomy group who did not withdraw consent were analysed in the interval appendicectomy group on an intention-to-treat (ITT) basis.

54 children were allocated to the active observation group. Two children became ineligible after allocation and were therefore withdrawn from the study by local investigators: one child developed a second, unrelated medical condition about 3 months after enrolment during the follow-up period that required several episodes of surgery and a second child developed an intra-abdominal abscess requiring re-admission and drainage 10 days after enrolment. The remaining 52 children were analysed in the active observation group on an ITT basis.

	Interval appendicectomy group (n=50)	Active observation group (n=52)
Age (years)	9 (5–12)	8 (4–11)
Male sex	25 (50%)	26 (50%)
Female sex	25 (50%)	26 (50%)
Presence of faecolith on imaging at initial presentation with appendix mass	11 (22%)	12 (23%)

Data are median (IQR) or n (%). Allocation to each treatment group within centre is shown in the appendix (p 1).

Table 1: **Baseline characteristics of treatment groups**

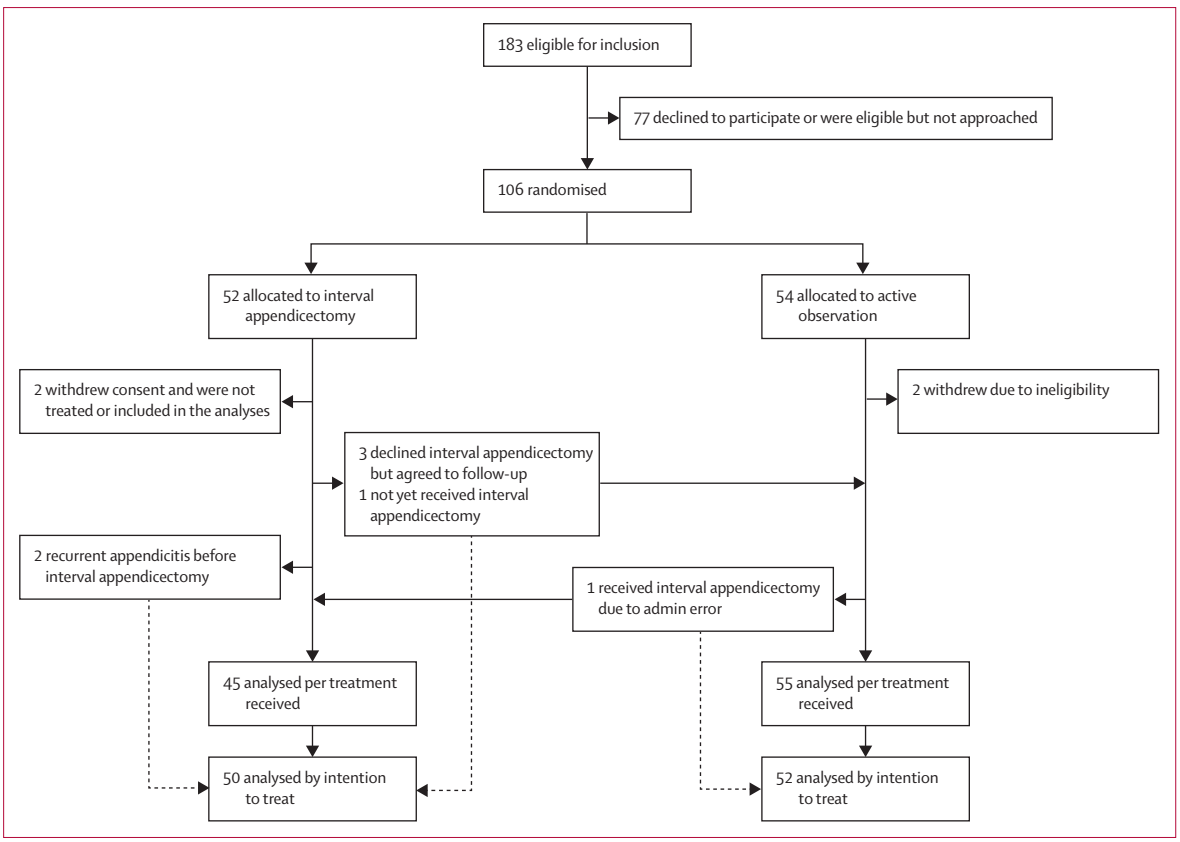

Figure: **Trial profile**

Of the 50 children allocated to the interval appendicectomy group and included in the ITT analysis, 44 children actually received interval appendicectomy during the study period. Interval appendicectomy was done at a median of 66 days (IQR 51–89) after treatment allocation. Severe complications related to interval appendicectomy occurred in three children (one port site herniation with small bowel obstruction requiring laparotomy, two with wound infection requiring antibiotics). The number of children meeting the protocol definition of the primary outcome (ie, severe complication) for the interval appendicectomy group was three (6% [95% CI 1–17]) of 50.

Of the 52 children in the active observation group, 51 children received active observation during the study period with a median duration of follow-up of 365 days (IQR 350–365) in those who did not undergo appendicectomy during follow-up. One child erroneously underwent interval appendicectomy without complications due to an administration error and was still counted in the ITT of the active observation group. Six (12% [95% CI 5–23]) of 52 children met the definition of the primary outcome in the active observation group in that they developed recurrent acute appendicitis and underwent appendicectomy with evidence of acute inflammation on histology. The patient who did not receive interval appendicectomy after 1 year was included in the per-treatment active observation group.

Secondary outcomes are reported in accordance with the protocol and were analysed initially on an ITT basis. In the interval appendicectomy group, two children developed recurrent appendicitis before their scheduled interval appendicectomy. One underwent laparoscopic appendicectomy, the other had a laparoscopic approach that converted to an open procedure and had a prolonged ileus (>72 h).

44 children allocated to interval appendicectomy group received interval appendicectomy. Of these, 43 appendicectomies were done with standard laparoscopy (including two conversions to open) and one with a single port technique. Median duration of surgery was 66 min (IQR 55–88) and median duration of hospital stay related to interval appendicectomy (not including admission to hospital for complications) was 32 h (IQR 28–48). 27 of the 44 families returned post-discharge diary cards in which the median time to return to school or normal daily activities after hospital discharge was 7 days (IQR 5–7). Histological reports were available for 42 of 44 surgical specimens, all of which contained appendiceal tissue, and revealed no inflammation in 15, acute inflammation in eight, chronic inflammation in 14, fibrosis in 17, and no carcinoid tumour in any of the specimens. Other histological findings included threadworms (n=2), lymphoid hyperplasia (n=2), eosinophilic infiltration (n=1), and granulomas in one child

	Interval appendicectomy (n=50)	Active observation (n=52)	p value*
Total length of stay (h)	32 (26–49)	0 (0–23)	<0·0001
Cost (UK£)	1476 (1022–2211)	0 (0–444)	<0·0001

Data are median (IQR). *Mann-Whitney test.

Table 2: **Comparison of total length of hospital stay in 1 year from enrolment and cost between treatment groups (intention-to-treat analysis)**

	Adjusted effect size (95% CI)	p value
Total hospital stay in 1 year follow-up (h)		
Sex		
Female	Reference	..
Male	1·28 (0·67–2·44)	0·46
Presence of faecolith		
No faecolith	Reference	..
Faecolith	2·65 (1·11–6·30)	0·028
Age (per year older)	0·93 (0·84–1·03)	0·18
Treatment group		
Interval appendicectomy	Reference	..
Active observation	0·10 (0·06–0·19)	<0·0001
Cost in 1 year of follow-up (UK£)		
Sex		
Female	Reference	..
Male	1·61 (0·50–5·23)	0·42
Presence of faecolith		
No faecolith	Reference	..
Faecolith	6·23 (1·30–30·2)	0·023
Age (per year older)	0·85 (0·70–1·02)	0·084
Treatment group		
Interval appendicectomy	Reference	..
Active observation	0·01 (0·00–0·02)	<0·0001

Effect sizes are multiplicative compared with reference as regression analysis was performed on log-transformed data.

Table 3: **Results of multiple linear regression analysis exploring relationship between treatment group and outcomes adjusting for minimisation factors (intention-to-treat analysis)**

who had a subsequently negative diagnostic evaluation for Crohn's disease. One minor adverse event was reported in the interval appendicectomy group in a child whose head was inadequately supported during anaesthesia. There was minor pain, but a satisfactory orthopaedic review and no sequelae.

In total, 12 (23%) of 52 children in the active observation group underwent appendicectomy. Six of these 12 had histologically confirmed recurrent acute appendicitis (the primary outcome for this group). The duration of the hospital stay related to recurrence was 105 h (IQR 95–140). Two children had a laparoscopic appendicectomy, one laparoscopic converted to open appendicectomy, and three open appendicectomy. Post-operative complications occurred in two children: one had a wound infection and one had prolonged (>72 h) ileus (no further surgery). At a median follow-up of 87 days (IQR 56–135) after recurrence, all six children were well but one had ongoing abdominal pain with exertion and one had unsatisfactory scar cosmesis. Histological assessment showed acute appendicitis in all six children with recurrent acute appendicitis, with a faecolith noted in two specimens (both had been positively identified on imaging at time of initial presentation with appendix mass). In one specimen, part of the fallopian tube that had been inadvertently excised along with the appendix was identified.

During the follow-up period, a further five children in the active observation group underwent appendicectomy for either suspected acute appendicitis (n=4) or ongoing abdominal pain (n=1). Histological assessments were negative for acute inflammation in all specimens, but showed chronic inflammation (n=2), lymphoid hyperplasia (n=2), and serositis suggestive of an extra-appendiceal cause of inflammation (n=1). These children spent a median 50 h (IQR 32–50) in hospital and all recovered without complication. The final child in the active observation group who had appendicectomy had an elective interval appendicectomy due to an administration error. Seven of the 12 families returned post-discharge diary cards after appendicectomy in which the median time to return to school or normal daily activities after hospital discharge was 7 days (IQR 2–12). Additionally, five children had a hospital admission during the follow-up period for assessment of abdominal pain, all of which resulted in discharge home without appendicectomy (median 17 h [IQR 11–19]).

Cost and total duration of hospital stay related to appendicitis within 1 year from enrolment were compared between interval appendicectomy and active observation groups, on an intention-to-treat basis. Summary statistics for these parameters are shown in table 2. Active observation was associated with a significantly shorter length of hospital stay and significantly lower cost than routine interval appendicectomy on univariate analysis. Multiple linear regression analysis was used to explore the relationship between treatment group and these outcomes, taking into account the minimisation criteria of age, sex, presence of a faecolith, and centre (table 3). There was no significant effect of treatment centre on either total length of stay or cost (data not shown). Children allocated to receive active observation spent on average 10% of the time in hospital that those allocated to interval appendicectomy spent during the first year after enrolment, and the cost was on average 1% of the cost of those allocated to interval appendicectomy. Children with a faecolith spent on average 2·6 times longer in hospital than those without, and the cost of treating these children was on average 6·3 times that of those without a faecolith.

Because not all children received their allocated intervention, a secondary analysis based on the treatment actually received was done. Outcomes were compared for 45 children who underwent interval appendicectomy and 55 who received active observation. Baseline characteristics between these groups were similar (appendix p 2).

In the 45 children who actually received interval appendicectomy, three (7% [95% CI 2–19]) met the criteria for the primary outcome in that they developed a severe complication after interval appendicectomy. In the active observation group, six (11% [95% CI 5–22]) of 55 children developed histologically proven recurrent acute appendicitis within the 1 year follow-up period. A further five children underwent appendicectomy for acute or chronic abdominal pain. Therefore, 11 children in the active observation group underwent appendicectomy in the 1 year follow-up period (20% [95% CI 11–33]).

In this analysis, both total length of hospital stay and cost were significantly lower in the active observation group compared with interval appendicectomy group in both univariate and multivariate analysis (appendix p 2). As in the ITT analysis, there was a statistically significant relationship between presence of a faecolith and cost of treatment (appendix p 2).

Additionally, we explored whether there was any difference in incidence of histologically proven recurrent appendicitis or appendicectomy within 1 year of enrolment in children allocated to active observation (ITT) or receiving active observation depending on sex and presence of a faecolith. The incidence of both these outcomes was similar regardless of sex and presence of faecolith in both ITT (appendix pp 3, 4) and per treatment received analyses.

Discussion

The main results of our study are that, in children under active observation, 12% developed histologically proven recurrent appendicitis and 23% had an appendicectomy within 1 year of randomisation. The presence of a faecolith had no influence on the frequency of either of these outcomes. Although interval appendicectomy carried a low severe complication rate (6%), complications in the general population could be substantial; one patient needed further surgery in this trial. Overall, the cost of active observation was less than that of interval appendicectomy.

Data were acquired from a population of children who initially presented with an appendix mass, were successfully treated without appendicectomy (or any other appendix-related procedure), and subsequently allocated to either 1 year of active observation or planned elective interval appendicectomy. The study design allows for truly comparative data to be obtained, minimising the influence of bias that might exist if data were recorded from observational cohorts only. Treatment groups were well matched for age, sex, and presence of a faecolith.

Before starting this study, we undertook a systematic review of the existing literature.[7] The volume of relevant literature was small, with only three articles reporting on rate of recurrent appendicitis in this specific patient population.[8–10] The overall weighted proportion of patients with recurrence based on these previous data was 21%. In this prospective study, we now report the incidence of recurrent appendicitis, as defined by histological examination of the appendix, as 12%.

Appendicectomy is a frequent procedure in general paediatric surgical practice and all surgeons were experienced in the procedure at the start of the study. Although our study confirms previous reports that interval appendicectomy is generally a safe procedure with low morbidity, it is noteworthy that one child in this study had a substantial complication of a laparoscopic port-site hernia requiring subsequent bowel resection. Two further children developed wound infections requiring treatment with antibiotics. Avoidance of interval appendicectomy would have avoided exposure to these complications but carries the risk of recurrence. Unexpectedly, two children developed recurrent appendicitis before their planned interval appendicectomy having previously had complete resolution of symptoms of appendix mass. Most surgeons will delay interval appendicectomy by a number of months to allow peritoneal inflammation to subside after the initial presentation. Our study shows that recurrence during this interval is possible.

With respect to missing an alternative diagnosis in children undergoing active observation, the most important issue to be aware of is that of a carcinoid tumour of the appendix. No child in this study who underwent appendicectomy, whether planned or unplanned, had a carcinoid tumour. Our previous systematic review estimated the risk of carcinoid tumour in this population as less than 1%, which is similar to that of previous series of appendicectomies.[11] This value is within the range of overall incidence in the general population of developing a carcinoid tumour at any site.[12]

In this study, we have shown the cost of active observation to be significantly less than that of interval appendicectomy. Although we did not undertake a full cost-effectiveness analysis, we included the most significant health-care-associated costs related to each treatment approach, including both scheduled and unscheduled hospital attendances and admissions. We did not, however, include costs related to visits to the general practitioner or other health-care-related costs. We acknowledge that with decreasing admission times related to interval appendicectomy the cost of interval appendicectomy could be reduced further. In this study, centres were free to use their standard practice including day case surgery if appropriate. In our analysis, both duration of hospital stay and time spent away from normal daily activities were significantly less for children in the active observation group than in the interval appendicectomy group. We did not include the additional effect of these factors on parental activity, such as days absent from work. These results are similar to a previous study that investigated the cost of interval appendicectomy after perforated acute appendicitis.[13]

In addition to children who had an appendicectomy during the 1 year follow-up period for histologically proven acute appendicitis, a further five children

underwent appendicectomy for either acute or chronic abdominal pain. Histological examination of these appendices did not reveal acute inflammation. Thus, 11 children in the active observation group underwent symptomatic appendicectomy. Despite this, more than 75% of children in the active observation group did not undergo appendicectomy within 1 year. This value is likely to be a pragmatic statistic to use for the purposes of counselling parents.

We did not detect an increased incidence of recurrent appendicitis in children who had a faecolith. A previous report suggested that a faecolith might increase the risk of recurrence[9] and, for this reason, we specifically included it as one of the minimisation criteria. Of the 12 children with a faecolith allocated to active observation, two (17%) developed histologically proven recurrent appendicitis during the follow-up period and one additional child underwent appendicectomy for a second episode of acute right iliac fossa pain 6 months after enrolment (histology showed lymphoid hyperplasia only with no inflammation), yielding an appendectomy rate of 25%. Across both treatment groups, the cost of treating children with a faecolith was significantly higher than that of treating children without a faecolith. However, the additional cost associated with treating a child with a faecolith was less than the cost benefit of active observation (compared with interval appendicectomy).

The strengths of this study are principally in its design. To our knowledge, this is the first prospective study to report on outcomes of children with an appendix mass and is also the only randomised study designed to address this important clinical question. The study was done at multiple centres making it probable that our findings are generalisable to the target population. The principal limitation is that children in the active observation group were followed up for only 1 year, while the risk of recurrent appendicitis or need for subsequent appendicectomy is clearly lifelong. We intend to follow these children up in the future for a total of 5 years after initial enrolment. An additional limitation is that we were unable to blind participants or observers to the allocated treatment due to the nature of the interventions. However, all outcomes were assessed with predefined, objective criteria. Furthermore, recruiting surgeons did not have access to patient allocation data, aggregated data, or data other than individual patient data in the course of usual clinical care.

In conclusion, this prospective randomised study has provided high-quality data with which clinicians, parents, and children can, for the first time, make an evidence-based decision regarding the justification for interval appendicectomy. In children who do not have routine interval appendicectomy, the risk of recurrent histologically confirmed appendicitis is 12% in the first year and more than 75% of children will have avoided appendicectomy 1 year later. Observation alone results in fewer days in hospital, fewer days away from normal daily activities, and is cheaper than routine interval appendicectomy.

Contributors

NJH conceived and designed the study, was the study coordinator, analysed data, interpreted data, wrote the draft of the manuscript, and approved the final manuscript submitted. SE designed the study, provided data analysis for the Trial Steering Committee, did the statistical analysis, created figures, interpreted the data, revised the manuscript, and approved the final manuscript submitted. MPS designed the study, recruited patients, collected data, revised the manuscript, and approved the final manuscript submitted. AP conceived and designed the study, recruited patients, collected data, revised the manuscript, and approved the final manuscript submitted. DMB conceived and designed the study, recruited patients, assisted with data collection, revised the manuscript, and approved the final manuscript submitted.

Declaration of interests

We declare no competing interests.

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