Outcomes 1 year after non-operative management of uncomplicated appendicitis in children: the Children with AppendicitiS during the CoronAvirus panDEmic (CASCADE) study

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Funding: No funding was received for this research.

Conflicts of interest: None

Category: Original article

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Abstract

Background

A major shift in treatment of appendicitis occurred early in the SARS-CoV-2 pandemic with non-operative management (NOM) used commonly outside research protocols and in units with limited prior experience. This study aims to compare real-world outcomes of surgery versus NOM of uncomplicated appendicitis in children with one year follow-up.

Method

A prospective multicentre observational study of children treated for uncomplicated appendicitis at 74 hospitals in the UK and Ireland from 1st April to 31st July 2020 was performed. Propensity-score matched (PSM) analysis was conducted using age, sex, C-reactive protein at diagnosis and duration of symptoms as covariates. Primary outcomes were success of NOM defined as achieving 1 year follow-up without undergoing appendicectomy due to recurrent appendicitis or ongoing symptoms and occurrence of any pre-defined complication (intra-abdominal collection, wound infection, bowel obstruction, or re-intervention).

Results

Of 1464 children with presumed uncomplicated appendicitis, 1027 (70.2%) underwent surgery and 437 (29.9%) underwent NOM. Ninety-four children (21.5%) treated by initial NOM required appendicectomy during the index hospital admission while recurrent appendicitis after discharge occurred in 25 (10.4%) children within one year. The overall success rate of NOM at 1-year was 63.1% (95% CI 58.0-68.3%). For PSM analyses, 688 children undergoing surgery and 307 undergoing NOM were included. Any pre-defined complication occurred in 50 (7.3%) children undergoing surgery and in 4 (1.3%) children undergoing NOM (OR 5.9 (95% CI 2.1-16.6)) in the PSM-cohort. There was no mortality or stoma formation.

Conclusion

NOM is a safe and valid alternative to appendicectomy in children with uncomplicated appendicitis.

Introduction

Non-operative management (NOM) of appendicitis in children has gained increased interest in recent years. Whilst prospective randomised trials are ongoing (1, 2, 3), existing data suggest that NOM is both safe and effective in most children with uncomplicated appendicitis.(4, 5) In the United Kingdom (UK), NOM of acute appendicitis was largely limited to the setting of a single feasibility randomised controlled trial (RCT) prior to the SARS-CoV-2 pandemic.(1, 6) During the pandemic, there was a paradigm shift in practice which we have previously documented and this provides an important opportunity to observe outcomes of NOM in the UK, in a real world setting.(7) We have previously reported initial short term outcomes of NOM during the pandemic demonstrating that 78% of children with either uncomplicated or complicated appendicitis were discharged home without requirement for appendicectomy.(8) However, knowledge of longer term outcomes of NOM is critical in informing treatment decisions by surgeons, patients and families.

The aim of this study was to report outcomes at one year in a cohort of children treated with either NOM or appendicectomy during the SARS-CoV-2 pandemic. Since the main focus of paediatric RCTs of NOM of appendicitis has been children with uncomplicated appendicitis, and it is for uncomplicated appendicitis that there is greatest interest in understanding the role of NOM as an alternative to appendicectomy, we restricted our analysis to cases with uncomplicated appendicitis.(1, 2, 3, 5, 9, 10)

Methods

Study design and inclusion criteria

Methods have been described in full previously.(7) In brief, this was a prospective multicentre observational cohort study of children aged less than 16 years at time of hospital admission with a diagnosis of acute appendicitis. Full study protocol can be found in the Supplementary materials. All hospitals in the UK and Ireland, including district general hospitals and specialist paediatric surgery centres, were eligible for participation. No changes to diagnostic or treatment pathways were required for inclusion in this study and no specific treatment protocols dictated either appendicectomy or NOM. This study has been reported as per the STROBE statement (supplementary material).

The diagnosis of appendicitis was based on clinical and/or radiological criteria and only children who were deemed to have uncomplicated appendicitis by the treating surgeon were included in the analysis. Uncomplicated appendicitis was defined as a clinical diagnosis of acute appendicitis by the treating surgeon without suspicion of gangrenous or perforated appendicitis or appendix mass. Children who presented with abdominal pain which was not thought to be appendicitis were excluded,

however, those treated for uncomplicated appendicitis initially but then given an alternative diagnosis were included in an intention to treat approach. This study includes all children with an initial admission date between April 1st and July 31st 2020. Follow-up was censored at 1 year post initial hospital admission date.

Ethical considerations

This study was registered at each site as a service evaluation, as defined by the health research authority guidance, as this was an observational study only collecting routine anonymised data with no change to clinical care pathways. Given this, individual patient consent was not required.

Outcomes

Outcomes were taken from a core outcome set of paediatric appendicitis.(11) The primary outcomes were any complication (defined as intra-abdominal collection, wound infection, bowel obstruction and/or re-intervention) and success of NOM. Re-intervention was defined as a subsequent abdominal surgical or radiological procedure requiring general anaesthesia beyond the initial procedure. Successful NOM was defined as children achieving 1 year follow-up without undergoing appendicectomy due to recurrent appendicitis or ongoing symptoms. Recurrent appendicitis was taken as the diagnosis made by the treating clinician with or without use of imaging. Secondary outcomes were individual complications (including re-intervention, intra-abdominal collection, wound infection, bowel obstruction, stoma formation and mortality), readmission, unplanned general anaesthetic, and length of stay. Appendicectomy for recurrent appendicitis in a child initially treated successfully with NOM was not considered as a complication since it is an anticipated event in this treatment pathway.

Data collection and analysis

Anonymous data were collected by local study teams within each hospital and submitted to the study team monthly with exclusion of duplicates as reported previously.(7, 8) Local study teams also returned follow-up data at one year post initial hospital admission.

Data are presented as mean (95% CI), median (IQR or range if specified) and/or number/total (%) as appropriate. Fisher's exact test or chi-squared test were used for comparison of categorical data and the Mann Whitney-U test was used for non-parametric continuous data. A two-tailed *p* value of less than 0.05 was considered as statistically significant. Comparison of outcomes for demographically and clinically matched children treated operatively versus NOM was performed using matched propensity-score analysis.(12) Children were matched using age, sex, admission C-reactive protein (CRP) and duration of symptoms using one-to-many matching within a calliper of 0.05 hence excluding those

without a matched patient in the other treatment group.(12) These variables were used to allow matching of demographics (age and sex) and disease severity (CRP and duration of symptoms). Following matching, conditional logistic regression or linear regression analysis were undertaken, with results for each outcome reported as odds ratios or days difference with 95% confidence intervals (CI) respectively. Statistical analysis was performed using StataSE v16 (StataCorp LLC, Texas, USA) and commands psmatch2 and stddiff were used for propensity score analyses. The study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies.(13)

Results

Children included, treatment method, and follow-up

A total of 2002 children from 74 hospitals with appendicitis were reported during the study period of whom 1464 (73.1%) were deemed to have uncomplicated appendicitis and included in the current analysis. Of these 1027 (70.2%) were treated operatively whist 437 (29.9%) underwent NOM. Children treated with NOM had a lower CRP and WCC at diagnosis than those treated operatively and were more likely to have had diagnostic ultrasonography (Table 1). At one year post hospital admission data were available for analysis from 1050 of these children (71.7%), including 316 children in the NOM group. Evaluation of differences between cases with and without follow up data at 1 year analysis (Table 2), indicated those with follow up were more likely to have been treated by a specialist paediatric surgeon, have had a diagnostic ultrasound and, if treated operatively, had undergone laparoscopic rather than open appendicectomy.

Operative management

There were 1027 children with suspected uncomplicated appendicitis who had operative management, of whom 655 (63.4%) had a laparoscopic procedure. Intra-operative findings were normal appendix in 57 (5.6%), uncomplicated appendicitis in 683 (67.4%) and complicated appendicitis in 273 (26.9%). Of these, 1-year follow up data were available for 734 cases (71.5%). Sixty four (8.7%) children had a related hospital readmission within the first year (median of 1 episode (range 1-4)) with a median time to readmission of 6 days (IQR 3-11, range 1-137). Of these, 29 (4.0%) children had symptoms including abdominal pain but no diagnosed complication.

Non-operative management

There were 437 children treated with NOM (Figure 1). Ninety four (21.5%) underwent appendicectomy within the index hospital admission with intra-operative findings of normal appendix in 6 (6.4%) children, uncomplicated appendicitis in 45 (47.9%) and complicated appendicitis in 43

(45.7%). Of the remainder, follow-up data were available for 240 children, with 50 (20.8%) re-admitted within 1 year (Figure 1), median time to readmission 48 days (7.5-144). The median number of readmissions was 1 (range 1-4). Recurrent acute appendicitis was treated in 25/240 (10.4%) children, with 21 undergoing appendicectomy, non-operative management in 3 children, and unspecified/ missing management in 1. Other reasons for readmission included abdominal pain and/or fever without a subsequent diagnosis of recurrent appendicitis (n=17), elective appendicectomy for ongoing symptoms but without acute appendicitis (n=4), and planned elective appendicectomy without symptoms (n=4). All appendicectomies after discharge following NOM were performed laparoscopically. In the 94 children who had undergone appendicectomy during initial admission and the 21 who underwent appendicectomy due to recurrent appendicitis intra-abdominal collection occurred in two children (1.7%), wound infection in one (0.9%), bowel obstruction in one (0.9%) and re-intervention was required in one child (0.9%) meaning any complication occurred in 4 children (3.5%). In total 123 children underwent appendicectomy within 1 year of index NOM. The overall success rate of NOM, defined as those achieving 1 year follow-up without undergoing appendicectomy due to recurrent appendicitis or ongoing symptoms, was 63.1% (95% CI 58.0-68.3% [211/334]).

Comparison of surgical versus non-operative management

Outcomes for children treated operatively and NOM were compared in a matched propensity-score analysis. Matching was possible using the pre-defined variables in 995/1050 (94.7%) children. Surgical treatment compared to NOM was associated with greater odds of any complication (OR 5.9 [95%CI 2.1-16.6]), intra-abdominal collection (OR 5.5 [95%CI 1.3-23.5]) and wound infection (OR 7.8 [95%CI 1.03-58.5]) but lower odds of unplanned general anaesthetic (OR 0.05 [95%CI 0.03-0.10]) and readmission (OR 0.51 [95%CI 0.34-0.77]) (Table 3). There were no deaths or stoma formation in either group or allergic reactions secondary to antibiotic use.

Discussion

This multicentre prospective cohort study compared outcomes of operative versus NOM of uncomplicated appendicitis in children with follow-up to one year following initial hospital admission. At 1 year, the success of NOM was over 60% and operative management was associated with significantly increased odds of developing any complication compared to NOM. These data will be useful for counselling children and families when deciding on treatment approach in this common surgical condition.

The success of NOM demonstrated in this study (63.1%) was similar to a large patient preference controlled study from the United States where the success rate was 67.1%.(4) The exclusion criteria

they used meant that only 19.1% of children with appendicitis approached were included in the study. In our observational study, children were included if the treating clinician deemed that the child had uncomplicated appendicitis with no requirement for diagnostic imaging or specific laboratory parameters. This pragmatic approach does mean that some children included had complicated appendicitis and it is possible that the NOM success rate may have been higher if more selective criteria were used. Supporting this, a success rate of 90% at 1 year has been achieved within the confines of a RCT.(9) On the other hand, children without appendicitis may have been included in the NOM group, which might inflate the apparent success rate. Despite this, this figure should be generalisable to all types of surgical centre within the UK and Ireland and provides a benchmark for success of NOM. Of note, the given overall success rate of NOM excludes those without 1 year follow-up, which is an unavoidable limitation of this study, but results in some uncertainty to the stated outcomes.

As expected in this study of uncomplicated appendicitis, complications were rare in both groups, with reintervention being required in less than 2% of children. Whilst this is reassuring, complications occurred more frequently in the operative group. A recent study exploring patient and parental attitudes of NOM of uncomplicated appendicitis found that a third of participants had a preference for NOM and avoiding complications of surgery (bleeding and infection) was the second most frequently expressed reason for this preference.(14) With the results of this current direct comparison of complications, there may be greater desire for NOM from children and parents. Readmission and need for unplanned general anaesthetic were seen more frequently in the NOM group, as would be expected, given the recognised risk of recurrence. Parental preference for NOM is reported as up to 63% despite this known risk.(15) Operative complications including intra-abdominal collection and wound infection were seen more commonly with surgical management. These data can be used when discussing management with children and families, and can inform shared decision making as each individual patient and family may have differing perceptions of the risks and benefits of each approach. Indeed, different preferences and perception of risk have been reported in qualitative work with families who were approached for participation in a RCT of NOM versus operative management of appendicitis in children.(16) These comparative data may also be of interest to hospitals and healthcare systems. Studies of adults with appendicitis have revealed cost differences between treatment approaches in favour of NOM.(17) Further work is needed to confirm whether this finding holds true in children.(18)

Outcomes at one year following NOM showed no unexpected adverse effects. Those managed by NOM who later required appendicectomy predominantly underwent this via a laparoscopic approach with few post-operative complications and only one of which required re-intervention. These findings

are similar to those reported by a similar study undertaken during the COVID-19 pandemic in adults which reported no adverse effects but did report 1.3% rate of subsequent malignancy in this adult population.(17) Fortunately, malignancy of the appendix is much rarer in children, is more commonly associated with complicated appendicitis and has an excellent prognosis.(19, 20) As data on NOM for uncomplicated appendicitis in children evolves, treatment without hospital admission may be considered appropriate, mirroring studies of outpatient antibiotic management of adult appendicitis.(21)

This study is limited by its observational nature, meaning that randomisation or treatment protocolisation did not occur. Thresholds for converting from NOM to appendicectomy are likely to have varied from surgeon to surgeon. Whilst we have used propensity scoring to provide a matched comparison, we cannot adjust for variables that were not measured or subjective variables. The benefit of our approach is that we can report on outcomes of a pragmatic study with a relatively large sample size achieved in a short time frame in a real-world setting. Inevitably, data for all cases were not available for inclusion in the one year analysis, despite best efforts to obtain them. Patient characteristics were similar for children whom data were and were not available at one year however those with follow-up were more likely to be treated by a specialist paediatric surgeon, have had a diagnostic ultrasound and undergone laparoscopic appendicectomy if treated operatively. We do not believe this has had a significant impact on our results, which remain generalisable. A final limitation is that although cases were included on the presumption that they had uncomplicated appendicitis, the lack of objective criteria for making this assessment and lack of surrounding evidence base, specifically in children, meant that some in the surgically treated group had more advanced disease and some did not have appendicitis at all. We cannot be certain of what proportion of the non-operative treatment group fell into either of these categories and whether complications, such as collections, developed before or after starting treatment. These limitations mean that caution should be exercised when comparing the data reported here with those obtained in prospective RCTs in which diagnosis, case selection and assignment to treatment groups may be more rigorously identified and controlled. Whilst we consider it a strength that we report outcomes to 1 year (one of the longest follow up periods for such a large cohort of children), longer follow-up is required particularly in the NOM group to understand whether there is late disease recurrence and the impact of this.

Figure legend

Figure 1 - Flow diagram of initial non-operative treatment of appendicitis.

Footnote

Code used for data analysis and dataset are available by reasonable request to corresponding author.

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Table 1. Clinical characteristics and investigation of children treated with operative versus non-operative management

		Operative (n=1027)	Non operative (n=437)	P
Age, median (IQR)	Years	11 (8-13)	11 (9-13)	0.69
Male		635 (61.8)	264 (60.4)	0.61
Speciality	GS	460 (44.8)	211 (48.3)	0.22
	SPS	567 (55.2)	226 (51.7)	
Laboratory values on admission, median (IQR)	WCC – $x10^9$/L	14.8 (11.8-17.8)	13.7 (9.9-16.9)	**0.0001**
	CRP - mg/L	29 (9-69)	21 (5-52)	**0.0008**
US performed		441 (42.9)	264 (60.4)	**<0.0001**
CT/MRI performed		27 (2.6)	13 (3.0)	0.71

Table 1. Clinical characteristics and investigation of children treated with operative versus non-operative management. Values are median [inter-quartile range] or n (%). GS – general surgeon; SPS – specialist paediatric surgeon; WCC – white cell count; CRP – C-reactive protein; L – litre; mg – milligrams; US – ultrasound; CT – computer tomography; MRI – magnetic resonance imaging.

Table 2. Clinical characteristics and management of children with and without 1 year follow-up				
		Follow-up (n=1050)	**No follow-up (n=414)**	**P**
Age, median (IQR)	Years	11 (8-13)	11 (8-13)	0.77
Male		640 (60.1)	259 (62.6)	0.57
Speciality	GS	435 (41.4)	236 (57.0)	**<0.0001**
	SPS	615 (58.6)	178 (43.0)	
Laboratory values on admission, median (IQR)	WCC – $x10^9$/L	14.3 (11.0-17.3)	14.9 (11.8-17.8)	0.08
	CRP - mg/L	25 (8-62)	29 (7-69)	0.39
US performed		556 (53.0)	149 (36.0)	**<0.0001**
CT/MRI performed		26 (2.5)	14 (3.4)	0.34
Non-operative management		316 (30.1)	121 (29.2)	0.74
Laparoscopic appendicectomy$^{\$}$		506 (69.8)	149 (51.2)	**<0.0001**

Table 2. Clinical characteristics and management of children with and without 1 year follow-up. Values are median [inter-quartile range] or n (%). GS - general surgery; SPS - specialist paediatric surgery; WCC - white cell count; CRP - c-reactive protein; US – ultrasound; CT – computer tomography; MRI – magnetic resonance imaging. $-initial operative management.

Table 3. Outcomes of children treated with operative versus non-operative management - matched propensity-score analysis			
	Operative (n=688)	**Non-operative (n=307)**	**Odds ratio or mean difference* (95% CI)**
Any complication (re-intervention, collection, wound infection, bowel obstruction)	50 (7.3)	4 (1.3)	**5.9 (2.1-16.6)**
Re-intervention	12 (1.7)	1 (0.3)	5.4 (0.70-42.0)
Intra-abdominal collection	24 (3.5)	2 (0.6)	**5.5 (1.3-23.5)**
Wound infection	17 (2.5)	1 (0.3)	**7.8 (1.03-58.5)**
Bowel obstruction	10 (1.5)	1 (0.3)	4.5 (0.57-35.4)
Stoma formation	0 (0)	0 (0)	0.44 (0.01-22.6)
Mortality	0 (0)	0 (0)	0.44 (0.01-22.6)
Readmission	60 (8.7)	48 (15.6)	**0.51 (0.34-0.77)**
Unplanned general anaesthetic	12 (1.7)	76 (24.7)	**0.05 (0.03-0.10)**
Initial hospital stay, days, median [IQR]	2 [2-4]	2 [1-3]	0.20* (-0.33-0.74)

Table 3. Outcomes of children treated with operative versus non-operative management - matched propensity-score analysis. Values are n (%) unless otherwise indicated. Odds ratios in bold are statistically significant ($p<0.05$). CI = confidence interval. * = mean difference.