CHAPTER 8

Long-term outcome of initial non-operative treatment strategy and immediate appendectomy for acute simple appendicitis in children

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Abstract

Background

The long-term outcome of initially non-operative treatment for simple appendicitis in children is unknown. We aimed to compare the long-term outcome of initially non-operative treatment with immediate appendectomy.

Methods

Between September 2012 and June 2014 children aged 7-17 years with a radiologically confirmed simple appendicitis were invited to participate in a multicentre prospective cohort study in which they were treated with an initially non-operative treatment strategy consisting of administration of antibiotics, analgesics and clinical observation for 48 hours; nonparticipants underwent immediate appendectomy. In October 2015, their rates of complications and subsequent appendectomies, and health-related quality of life (HRQOL) were assessed for all children through a telephone interview, HRQOL questionnaire, and review of the medical charts.

Results

Overall, 44 children were included, of whom 25 were treated with an initially non-operative treatment strategy and 19 with immediate appendectomy; median (range) follow-up was 25 (16-36) and 26 (17-34) months, respectively. The percentage of patients [95%CI] experiencing complications in the initially non-operative group and the immediate appendectomy group was 12 [95%CI: 4–30]% and 11 [95%CI: 3–31]%, respectively. At 25 months, appendectomy could be avoided in 19 of the 25 children (76%); none of the 6 patients operated subsequently experienced any postappendectomy complications after delayed appendectomy. Response rate for the HRQOL in the non-operative treatment group and the appendectomy group was 68% and 21%, respectively. Overall, HRQOL in the non-operative treatment group was similar to that of healthy peers.

Conclusions

Long-term outcome of initially non-operative treatment for acute simple appendicitis in children is favourable and similar to the outcome in those who undergo immediate appendectomy.

Introduction

Appendectomy, as the standard of care for acute simple (uncomplicated) appendicitis, has become subject of debate in recent years. An initially non-operative treatment strategy consisting of antibiotics, analgesics, intravenous fluids and clinical monitoring has been suggested as an alternative. Meta-analyses from randomised trials performed in the adult population concluded that initially non-operative treatment can avoid appendectomy in 60-85% of patients at one year follow-up.[1-3] In addition, initially non-operative treatment leads to a reduction in the complication rate by 31-48%.[1,2,4,5] Other reported potential benefits from initially non-operative management are decreased utilisation of pain medication and reduction in costs.[1,6]

In the paediatric population, to date only pilot study results are available. Several cohort studies including sample sizes ranging from 12-78 patients have shown that in the short-term (maximum follow-up 8 weeks) appendectomy was avoided in more than 80% of paediatric patients.[7-15] At one year follow-up the percentage of paediatric patients in whom an appendectomy had been avoided ranged from 62 to 81%.[9,11,14,15]

The current study is a follow-up study of our study investigating the short-term results of a non-operative treatment strategy in a cohort of Dutch children aged 7-17 years.[7] The aim of the current study was to evaluate the long-term (> 1 year) outcome in terms of complications, avoidance of subsequent surgery and health-related quality of life (HRQOL) of an initially non-operative treatment strategy for acute simple appendicitis in children (7-17 years old), as compared with outcomes in those who were invited but underwent immediate appendectomy because the parents declined inclusion in the cohort.

Patients and methods

In October 2015, we contacted all patients who were eligible for the multicentre-prospective cohort study conducted between September 2012 and June 2014.[7] This study was performed in two academic (tertiary referral) centres and two large peripheral hospitals in the Netherlands. Inclusion and exclusion criteria for the cohort study are described in more detail in our previous publication. In summary, all children aged 7-17 years old with a simple appendicitis confirmed by imaging studies were eligible for inclusion. Excluded were children with signs of severe general illness, with a faecalith, or with significant comorbidity, and those with a known type 1 allergy for the antibiotics used.[7]

Simple appendicitis was defined in this study, as in our previous study, using both clinical and radiological variables.[7] Clinical criteria included:

- Unwell, but not generally ill;
- Localised tenderness in the right iliac fossa region;
- Normal/hyperactive bowel sounds;
- No mass palpable;
- No diffuse guarding.

Ultrasonography criteria included:

- Noncompressible appendix with an outer diameter of >6 mm;
- Hyperaemia within the appendiceal wall;
- Infiltration of the surrounding fat;
- No signs of perforation/abscess/mass/phlegmon/disseminated peritoneal fluid/extra-luminal gas.

For the current study, we compared the two patient groups:

1. *Initially non-operative treatment group*. Initially non-operative treatment strategy consisted of intravenous administration of antibiotics with inhospital monitoring, diet restriction and pain medication as needed. Study procedure is discussed in more detail in the original manuscript.[7]
2. *Immediate appendectomy group.* Patients who were eligible for initially non-operative treatment according to the study protocol, but whose parents declined participation, all underwent immediate appendectomy with pre-, peri- and postoperative care according to the national Dutch protocol.[16]

The research ethics committee of the VU University medical centre confirmed in writing that the Netherlands' Medical Research Involving Human Subjects Act (WMO) did not apply to this follow-up study and waived the need for official research ethics approval for this part of the study. The original cohort study was approved by the medical ethics committee of the VU University medical centre.[7]

Study procedure

The legal guardians from eligible patients were contacted by the study coordinators (RG and FH) and asked for informed consent by telephone in October 2015. When informed consent was obtained, a scheduled telephone interview was held, assessing the patient's course after the initial treatment strategy in order to detect any adverse outcome. Specific questions asked were, but not limited to, the following: "Did your son/daughter undergo an appendectomy after the initially non-operative treatment strategy?" "Did any complications related to the non-

operative or operative treatment occur in the months after the initial treatment?" In addition, the legal guardian's permission was asked to review the patient's medical chart. Finally, an information letter including a statement of written consent was sent to the patients' home address together with the Child Health Questionnaire Child Form 87 (CHQ-CF87) for patients ≥ 10 years or the Parent Form 50 (CHQ-PF50) for patients < 10 years (see below); families were asked to fill out these forms and return them to the coordinator by regular mail or email. If after three weeks no response was received, patients were contacted once more by telephone by the study coordinator to inquire about the status of the questionnaires. Analysis of all received questionnaires was done one month after this second phone call.

Primary outcome

The primary outcome of the study was the percentage of patients experiencing complications after initially non-operative treatment strategy as compared to immediate appendectomy strategy during the period of at least one year after initial treatment.

Complications were defined as:

- Allergic reaction to antibiotics administered;
- Readmission to an emergency department or hospital for indications other than recurrent appendicitis, but potentially related to the appendicitis;
- Need for subsequent invasive interventions other than appendectomy, but related to appendicitis or to a postappendectomy complication; complications associated with immediate or delayed appendectomy being superficial site infection (SSI); intra-abdominal abscess (IAA); stump leakage and stump appendicitis; secondary or prolonged bowel obstruction; anaesthesia-related complications; incisional hernia; urinary tract infection and pneumonia.

Complications were classified according to the *Clavien-Dindo Scale*, which measures the severity of complications in a reproducible manner; its scores range from grade 1 to 5.[17] Major complications were defined as Clavien-Dindo grade 3 or more, grades lower than 3 were categorised as minor complications.

Secondary outcomes

In the initially non-operative treatment group, the following secondary outcomes were defined:

- Recurrent appendicitis: number of patients who experienced (histologically proven) recurrent appendicitis after completion of the total antibiotic course (after 7 days) during follow up;
- Interval appendectomy: number of patients who underwent appendectomy on parental request or were offered interval appendectomy, or who underwent delayed appendectomy

after completion of the initial antibiotic treatment without histological confirmation of acute appendicitis;
- Faecalith: number of patients who underwent appendectomy due to the fact that a faecalith was noted by ultrasound after 48 hours after start of the initially non-operative treatment strategy (study protocol for safety reasons);
- Total appendectomies: total number of patients who underwent appendectomy after initially non-operative treatment during follow-up.

HRQOL was assessed using the validated CHQ-CF87 questionnaire in both the non-operative and operative group.[18,19] This generic selfadministered tool is designed to measure various physical and psychosocial components of the health status of a child.[18-20] Domains and their subscales measured by the CHQ-CF87 are listed in appendix 1.[18,21] The questionnaire contains 87 questions with 4-6 response options. Scores from each question are transformed to a 0–100 scale, in which higher scores indicate greater well-being.[18,21] The CHQ-PF50 has been developed to assess the HRQOL from the parents' perspective, and was used in case the child was below 10 years of age.

HRQOL was assessed at the time of inclusion in the cohort study (T=0) in the initially non-operative treatment group and at the time of the present study (T=1) in both groups. In the initially non-operative treatment group the change in quality of life (delta HRQOL) was calculated of the patients with T=0 and T=1 measurements. We arbitrarily decided a minimum of 50% response rate to perform analysis at T=0 and T=1 in both the initially non-operative treatment group and the operative group.

Statistical analysis

The primary outcome is presented as number of patients and percentage with 95% confidence interval {95%CI}, calculated with PREZIES.[22] All secondary outcomes are displayed in the same manner as the primary outcome with the exception of HRQOL, which is displayed as median (minimum-maximum). As the number of patients in both groups was low, we performed descriptive analysis only. We used the statistical software package SPSS version 22.0 (Armonk NY: IBM Corp).

Results

In total, 44 patients were included in this study, of which 25 (57%) in the initially non-operative treatment group and 19 (43%) in the immediate appendectomy group, respectively. No children were lost to follow-up in either group.

The clinical characteristics of both groups at the time of follow-up are displayed in Table 1. Median (range) follow-up was 25 (16-36) and 26 (17-34) months for the initially non-operative treatment and immediate appendectomy group, respectively.

Table 1: Clinical characteristics on admission.

	Initially non-operative treatment N=25	Immediate appendectomy N=19
Age in years (median (range))	14 (10-17)	14 (7-17)
Male sex (N (%))	15 (60)	14 (74)
Simple appendicitis (N (%))	25 (100)	15 (79)
Complex appendicitis (N (%))	-	4 (21)
Follow up in months (median (range))	25 (16-36)	26 (17-34)

Primary outcome

The percentage of patients experiencing complications was 12% (3 out of 25 patients, [95%CI: 4–30%]) and 11% (2 out of 19 patients, [95%CI: 3–31%]), respectively, for the initially non-operative treatment and immediate appendectomy group. Three minor complications (one patient with readmission for gastroenteritis more than 6 months after initially non-operative treatment, one patient with a urinary tract infection within 8 weeks after discharge, and one patient with a possible allergic reaction to the administered antibiotics during the clinical admission phase) occurred in the initially non-operative treatment group during the follow-up period. In the immediate appendectomy group one minor (one patient with readmission for fever within 8 weeks after appendectomy) and one major complication during the clinical phase occurred. The major complication consisted of one patient with laryngospasm during extubation requiring reintubation and ICU admission for four days.

Secondary outcomes

Figure 1 displays the secondary outcomes for the non-operative treatment strategy. In 19/25 patients (76% [95%CI: 57-89%]) appendectomy had been avoided during a median (range) follow up of 25 (16-36) months. The indication to perform appendectomy was faecalith (N=1), interval appendectomy (N=2) and recurrent appendicitis (N=3). Reason to perform interval

appendectomy was on parental request in one patient and on doctor's request in another patient. The percentage of patients with recurrent appendicitis after initially non-operative treatment was 12%. None of the six patients who underwent delayed appendectomy experienced any postappendectomy complications, had perforating appendicitis or was diagnosed with an unexpected malignancy.

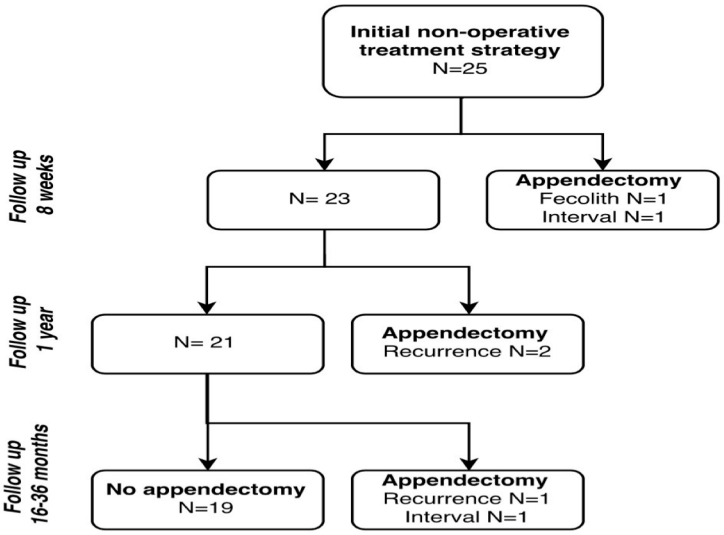

Figure 1: Inclusion, management, and follow-up strategy in the initially non-operative treatment group.

Health-related quality of life

The response rate to the HRQOL questionnaire in the initially non-operative treatment group was 16/25 (64%) at T=0 and 17/25 (68%) at T=1. All respondents in this group were older than 10 years old, and only the CHQ-CF87 was used. Unfortunately, and after reminders sent, the response rate in the immediate appendectomy group was only 4/19 (21%), so it was decided not to perform a comparative analysis. Table 2 shows the results of the HRQOL at T=0 and T=1 of the initially non-operative treatment group (N=16 and N=17 respectively for T=0 and T=1). In 11 patients in the initially non-operative treatment group delta HRQOL could be calculated. Delta HRQOL of the 11 patients is displayed in Table 3.

Table 2: HRQOL subdomain scores at follow up in the initially non-operative treatment group

	HRQOL T=0 N=16/25	HRQOL T=1 N=17/25
Physical functioning	100 (52 - 100)	100 (81 - 100)
Role functioning: Emotional	100 (44 - 100)	100 (78 - 100)
Role functioning: Behavioral	100 (33 - 100)	100 (67 - 100)
Role functioning: Physical	100 (33 - 100)	100 (67 - 100)
Bodily pain	70 (10-100)	80 (50 - 100)
Behavior	85 (75 - 97)	85 (53 - 99)
Mental health	70 (44 - 94)	75 (36 - 100)
Self-esteem	75 (48 - 96)	75 (38 - 89)
General health	76 (25 - 96)	75 (40 - 96)
Family activities	88 (58 - 100)	92 (67 - 100)
Change in health	1 (0 - 3)	2 (2 - 4)
Family cohesion	75 (50 - 100)	50 (25 - 100)

Results are displayed as median (range)

Table 3: HRQOL pre (T0) and post (T1) initially non-operative treatment (n=11/25)

	T=0 HRQOL	T=1 HRQOL	Delta HRQOL
Physical functioning	100 (52-100)	100 (82-100)	0 (-7-4)
Role Functioning: Emotional	100 (44-100)	100 (78-100)	0 (-56-11)
Role Functioning: Behavioral	100 (33-100)	100 (67-100)	0 (-33-33)
Role Functioning: Physical	100 (33-100)	100 (67-100)	0 (-55-33)
Bodily pain	70 (10-100)	80 (50-100)	10 (-30-20)
Behavior	85 (75-97)	85 (53-99)	0 (-21-33)
Mental health	77 (44-94)	73 (36-100)	-4 (-8-25)
Self-esteem	75 (48-96)	75 (38-89)	0 (-14-34)
General health	77 (25-96)	70 (40-96)	-7 (-29-31)
Family activities	88 (58-100)	92 (67-100)	0 (-42-17)
Change in health	2 (0-3)	2 (2-4)	0 (-2-1)
Family cohesion	75 (50-100)	50 (25-100)	0 (-50-50)

Results are displayed as median (range)

Discussion

This follow-up study shows that for children aged 7-17 years old with radiologically confirmed simple appendicitis, the percentage of patients experiencing complications is comparable for an initially non-operative treatment strategy as compared to an immediate appendectomy strategy. Initially non-operative treatment avoided appendectomy in 19 out of 25 patients (76%)

during a follow-up ranging between 16 and 36 months. Moreover, none of the six patients who underwent delayed appendectomy experienced any postappendectomy complications, nor suffered from perforated appendix or from unexpected malignancy. These results confirm the overall safety of a non-operative treatment approach for children with simple appendicitis.

The debate regarding the advantages of a generalised initially non-surgical approach with intravenous antibiotic treatment for children with acute simple appendicitis is still ongoing.[23] A major benefit of this strategy is the avoidance of surgery. In the short-term, studies show that it may avoid surgery in 83-99% of all children with simple appendicitis.[7-15] The main downside of this strategy is the potential need for appendectomy in the future. To date, only a few studies have reported long-term outcomes of this strategy in the paediatric population.[9,11,14,15] With an overall number of 155 observed children, these studies' results agree with our results and show that during one year of follow-up, appendectomy can be avoided in 62-81% of patients.[9,11,14,15]

An interesting phenomenon is the occurrence of delayed appendectomies in these studies. Indications for delayed appendectomy are interval appendectomy (on parents' request, a rare occurrence in our study) and recurrent appendicitis. In the study by Hartwich, all patients were offered interval appendectomy at 2 months follow-up.[10] We believe that in the near future the number of interval appendectomies will diminish as more evidence becomes available regarding the safety of initially non-operative treatment, leading to increasing confidence in this strategy. The percentage of children in our study experiencing recurrent appendicitis during 16-36 months of follow-up was 12%, which is consistent with the current literature, reporting a cumulative incidence ranging from 5-21% during one year follow-up.[11,14,15]

Discussion remains whether patients with faecaliths should be offered initially non-operative treatment strategy. In our own study, we decided to exclude patients with faecaliths, considering that faecaliths might be associated with a higher risk of failure of non-operative treatment.[7] This concept has recently been confirmed in a study by Mahida et al.[24] Their prospective nonrandomised trial investigating non-operative treatment in children 7-17 years of age with simple appendicitis and faecaliths was preliminary terminated because in 3 out of 5 patients (60%) delayed appendectomy was necessary.[24] In the studies by Svensson and by Tanaka patients with faecaliths were included. Respectively, 9/19 (47%) patients with a faecalith in the study by Tanaka and 3/5 (60%) in the study by Svensson required an appendectomy during the follow-up period.[11,15] When patients with faecaliths are excluded in future trials, the failure rate of initially non-operative treatment might be reduced. Preoperative imaging investigating the presence of faecaliths seems therefore crucial.

The potential benefits of an initially non-operative management strategy in children with acute simple appendicitis are currently debated. As appendectomy might be avoided with this new treatment strategy, children will no longer be exposed to the risk of postappendectomy complications, the occurrence of which has been reported to occur in up to 17% in children with acute simple appendicitis, depending on the surgical approach.[11,13,15,25] They mainly consist of superficial site infections, intra-abdominal abscesses and secondary bowel obstruction. It is debatable whether the latter can also be caused by appendicitis itself. In our study, 2 patients (11%) experienced postoperative complications after immediate appendectomy, of which one was minor while the other led to reintubation and ICU admission. The occurrence of complications associated with initially non-operative treatment ranges between 0 and 8% in children with acute simple appendicitis.[9-15] In our study, 3 patients (11%) experienced complications (readmission for gastroenteritis, urinary tract infection and allergic reaction to the administered antibiotics), although it is debatable what the relation and significance of the first two complications were; we feel that only the allergic reaction has a direct relationship to the initially non-operative treatment strategy. Moreover, all complications ware classified as minor. A potential downside of the non-operative treatment strategy is that it might contribute to the increasing problem of antibiotic resistance worldwide. Based upon this study, it is not possible to draw any conclusions on this topic. We emphasise that in this study appropriate antibiotics (for the expected bacteria) and combinational therapy were given, a well-known strategies to reduce to the risk of antibiotic resistance development.[26]

As more evidence becomes available regarding the initially non-operative treatment strategy in terms of safety, complications and avoidance of appendectomy, it is necessary to evaluate other potential advantages and disadvantages of this strategy. This is important to adequately inform patients and parents and to empower them in their decision-making. Quality-of-life outcomes may play a role in their considerations. In this study, HRQOL was assessed using a validated questionnaire for children. Unfortunately, due to a low response rate in the immediate appendectomy group formal statistical testing was considered useless. Low response rates were also noted in other studies investigating HRQOL in the paediatric population.[9,11,18,27,28] Explanations for these low response rates include, but are not limited to the time it takes to fill out the questionnaires, with general questions not related to any specific disease, and the time interval between initial appendicitis episode and the current study. Although two other studies investigated patient satisfaction and cost-utility associated with initially non-operative treatment of simple appendicitis in children,[10,11] to our knowledge only one study investigated HRQOL.[9] Minneci et al investigated HRQOL using the Pediatric Quality of Life Inventory Instruments at oneyear follow-up in 35 patients with non-operative treatment and 50 patients with operative treatment. Overall HRQOL reported by the children was similar for the non-operative and operative groups: 95.7 (89.1-98.9) versus 91.3 (87.0-98.9).[9] Due to the

use of different instruments, it is impossible to compare our study to the study of Minneci.[9] However, it appears that overall the HRQOL measured before and 16-36 months after initially non-operative treatment are comparable to those of reference populations.[18,20,28] This is not surprising, as appendicitis is an acute disease and QOL will improve after treatment. One might, however, argue that QOL might be reduced in the non-operative treatment group due to the fear of recurrent appendicitis. This seemed not to be the case in our study.
To our knowledge this is the first study investigating the change in HRQOL more than one year after initially non-operative treatment for acute simple appendicitis. Unfortunately neither this study nor any other studies have investigated the parental QOL. It is imaginable that QOL of parents of the non-operative treatment group might be reduced because recurrent abdominal pain in the child might lead to concern about the possibility of recurrent appendicitis. This needs to be explored in future studies.

Of interest, although all patients fulfilled the inclusion criteria for the multicentre prospective cohort study, complex appendicitis was still noted in 4 out of 19 patients (21%) during surgery in the patients who underwent immediate appendectomy. Apparently, it remains challenging to accurately distinguish simple from complex appendicitis before the operation. Although, therefore, it is plausible that some patients in our initially non-operative treatment group also suffered from complex appendicitis, all initially non-operated patients recovered and none of the patients who underwent a delayed appendectomy suffered from complex appendicitis. Further research should focus on biomarkers to accurately differentiate patients with simple and complex appendicitis. Research groups focusing on the initially non-operative treatment strategy might benefit from implementing available scoring systems (based upon preoperative variables) to differentiate simple from complex appendicitis. This might lead to a reduction in the risk of including patients with complex appendicitis.[29-31]

Our study has some limitations. First, the number of patients in this study is relatively small, leading to limited certainty regarding estimated outcome frequencies. When combining the results of all published follow-up studies, the results regarding the long-term safety of initially non-operative treatment of simple appendicitis are reassuring. Secondly, the low response rate regarding HRQOL in the initially operated group impairs comparison of this outcome between groups. Yet, because there is an external standard, HRQOL in our patients can be interpreted as normal. A third limitation is the timing of follow-up. After 12 months or more after their acute appendicitis, patients might not recall all adverse events or complications. This was obviated by reviewing the medical charts of the patients. Fourthly, the follow-up in the initially non-operative treatment strategy group ranged from 16-36 months and not all complications may have occurred yet. It is our plan to continue the follow up of this cohort of patients, to identify the outcome of the initially non-operative treatment strategy after 5 years.

These extended long-term results will help establish the value of the initially non-operative treatment strategy for acute simple appendicitis in children. Finally, outcomes such as medical consumption and costs, of interest in the decision making process, were not assessed in this study. Future studies should focus on these topics.

In conclusion, our study shows that the long-term outcome of initially non-operative treatment for acute simple appendicitis in children is favourable, with normal HRQOL after 16-36 months of follow-up. As the percentage of patients experiencing complications is comparable to that of those treated with immediate appendectomy, initially non-operative management seems to be able to avoid appendectomy in 3 out of 4 children.

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