

Delayed appendectomy in the pediatric patient. How safe is it?

Apendicectomía diferida en apendicitis aguda no complicada. ¿Es seguro en pediatría?

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What do we know about the subject matter of this study?

Acute appendicitis is the most frequent surgical emergency in the pediatric age group. There is controversy regarding the possibility of deferring surgery within 24 hours of diagnosis in stable patients versus performing it emergently.

What does this study contribute to what is already known?

In our series, deferred appendectomy in selected patients with uncomplicated acute appendicitis does not significantly increase hospital stay or postoperative complications.

Abstract

Delayed appendectomy is an option in centers where there is no pediatric surgeon on call. **Objective:** to analyze the results of delayed versus immediate surgery in non-complicated appendicitis in pediatric patients. **Patients and Method:** Analytical quasi-experimental study including appendectomies performed for uncomplicated appendicitis in children aged between 6 and 14 years. We compared the outcomes of the group of patients operated on at the time of diagnosis with those operated on the following day. Demographic and general variables and postoperative evolution were analyzed. The main variables were the length of stay and postoperative complications. We also analyzed factors related to the finding of gangrenous appendicitis during surgery. **Results:** Forty-five patients were included in the study, 21 in the immediate-surgery group (AIn) and 24 in the delayed-surgery group (ADif). The ADif group underwent surgery on average 21 hours after diagnosis. There were no significant differences in the mean length of stay and no significant increase in complications were detected in the ADif group. In the complementary analysis, the presence of appendicolith increased the probability of gangrenous appendicitis. **Conclusions:** Delaying appendectomy in selected patients with uncomplicated appendicitis did not significantly increase either hospital stay or complication rate in our series. If we correctly identify these patients, some referrals could be avoided since these entail stress for the family and overload referral centers.

Keywords:

Acute Appendicitis;
Appendectomy;
Laparoscopy;
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Introduction

Deferred appendectomy is a growing option in healthcare centers where pediatric surgery is not available on-call. After a determined hour in the afternoon, patients diagnosed with uncomplicated appendicitis are admitted with antibiotic therapy, analgesia, and stabilization, preparing them for surgery the next day^{1,2,3}. Most studies indicate that if complications occur, they are generally due to the diagnostic delay and the delay in starting the administration of intravenous antibiotics rather than to the final time from admission to surgery^{4,5,6}.

However, there is some reluctance in some centers to this approach and some studies find worse results when appendectomy is deferred, so they suggest the possibility that it would be better to operate on appendicitis emergently, even in the early morning, rather than waiting until the next day thus reducing the possibility of progression of appendicitis and the appearance of complications by shortening the time between arrival at the emergency department and the surgery^{7,8}.

In recent years, the classical theories that assumed that acute appendicitis is a process that evolves over time and inevitably leads to perforation have been revised. The role of the individual's immune response in the progression of appendicitis, rather than the time elapsed^{9,10,11}, is becoming increasingly important. Thus, the importance lies in correctly distinguishing patients who will require immediate surgery from those in whom surgery can be deferred¹², or even in considering purely conservative management^{13,14}.

The primary objective was to compare complications and length of hospital stay in children with uncomplicated acute appendicitis resolved in a deferred manner versus an immediate approach. The secondary objective was to identify early predictors of gangrenous appendicitis.

Patients and Method

Prospective quasi-experimental analytical study, conducted at the *Hospital Universitario Mútua de Terrassa*. Patients were admitted to the Pediatric Emergency Department with the diagnosis of abdominal pain and were referred to the Pediatric Surgery Department after the diagnosis of acute appendicitis.

Inclusion criteria were as follows: Patients aged 6 to 14 years with clinical, ultrasound, and analytical diagnosis of uncomplicated acute appendicitis who visited the Emergency Department between September 2009 and January 2016. Patients whose parents signed the informed consent for their participation (in both study groups) were included. Patients with signs of worsened

condition (more than 24 hours of symptoms, poor general condition or sepsis, presence of abscess or plastron or echogenic free fluid on ultrasound), presence of comorbidities, and those who did not consent were excluded. Patients who did not agree to participate in the study were referred if they were outside of the pediatric surgeon's office hours or were immediately operated on without including their data in the study.

The distribution in the study groups was made arbitrarily (convenience sampling) according to the time of the consultation and therefore the presence or not of a pediatric surgeon, since our center does not have 24-hour pediatric surgical continuity of care. In one group, the appendectomy was performed immediately (InA) because the patient arrived within the available hours of pediatric surgery and, in the other group, it was deferred to the next day (DeA).

The main variables were days of hospital stay and the appearance of complications. As control and descriptive variables, age, sex, hours of evolution since the onset of the symptoms, and clinical data (vomiting, fever, peritoneal irritation) were collected. Ultrasound data included appendiceal size, the presence of free fluid, fat involvement, and the presence of appendicolith. Analytical data included white blood cell count, the percentage of polymorphonuclear cells (PMN), and C-reactive protein (CRP) values. The hours elapsed from diagnosis to surgery and the type of appendix (macro and microscopic) data were also collected.

For the secondary objective, patients were divided according to the type of appendicitis found at surgery into phlegmonous/normal and gangrenous/perforated.

Protocol for diagnosis and management of acute appendicitis

All patients were evaluated and diagnosed in the Pediatric Emergency Department. All of them underwent blood tests and ultrasound which confirmed the diagnosis. They were indicated fasting and prophylactic antibiotic therapy was started with intravenous amoxicillin-clavulanic acid at 100 mg/kg/day dose. Pediatric surgery was contacted and, in case of availability, surgery was performed at the time of diagnosis when the patient completed 6 hours of preoperative fasting (InA Group). In case of unavailability of a pediatric surgeon, the patient remained hospitalized, and surgery was performed the next day (DeA Group).

All patients underwent laparoscopic appendectomy using a three-trocar approach as previously described¹⁵. If it was impossible to complete the laparoscopic technique due to anatomical or anesthetic reasons, conversion to open surgery was considered.

After surgery, in the case of phlegmonous appendicitis, patients received three doses of prophylactic

amoxicillin-clavulanic acid. In the case of circumscribed gangrenous appendicitis, they received antibiotic therapy with amoxicillin-clavulanic acid for 48-72 hours according to clinical evolution. In the case of widespread gangrenous appendicitis with free pus or perforated appendicitis, they received treatment with ceftriaxone and metronidazole or gentamicin and metronidazole for at least 5 days.

Statistical analysis

For the analysis, the data included in an Excel database were exported to the statistical software Stata/SE 13.0. From the analysis, qualitative variables were expressed by absolute number and percentage and qualitative variables by median and 25%-75% interquartile range (IQR). The independent or potentially confounding variables were compared between groups to determine their homogeneity using Fisher's exact test for the qualitative variables or the Mann-Whitney U test for the quantitative ones. To determine the differences between groups in the main outcome variables (complications and days of stay), Fisher's exact test and Mann-Whitney U test were used, respectively. For the secondary objective of determining the factors associated with gangrenous or perforated appendicitis (dichotomous dependent variable), a bivariate analysis was first performed using the Fisher's exact test or Mann-Whitney U test, as appropriate, and then a multivariate analysis was performed including the variables with a $p < 0.2$ in the bivariate or that were considered clinically significant. A $p < 0.05$ or a 95% confidence interval that did not include the unit was considered significant.

Ethical considerations

This study was approved by the Clinical Research Ethics Committee of our center. All the representatives of the participating patients received the pertinent information and signed informed consent for their inclusion in the study. Data processing was performed following the Organic Law 3/2018, of December 5, on the Protection of Personal Data, and EU Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016, which ensures the confidentiality of the personal data of the patients included in the study at all times.

Results

45 patients met the inclusion criteria. Among them, 21 were from the InA Group and 24 were from the DeA Group. Both groups were homogeneous in terms of baseline demographic characteristics, age, and sex. There were also no statistically significant differences

regarding clinical characteristics, hours of evolution and symptomatology, and ultrasound and analytical findings. Table 1 shows the results of these variables.

The median number of hours elapsed from diagnosis to surgery was 3h²⁻⁴ in the InA Group and 21h in the DeA Group¹⁹⁻²³.

Regarding the type of appendix according to surgical findings and pathological anatomy analysis, most cases were phlegmonous appendicitis, 13 (61.9%) and 16 (66.7%) cases in each study group. We found gangrenous appendicitis in 7 cases (33.3%) in the InA Group and 5 (20.8%) in the DeA group. There was one appendix without inflammation data in the InA group and two in the DeA group as well as one case of perforated appendix. No statistically significant differences were found in these data between the two groups ($p = 0.7$). Figure 1 summarizes the percentages.

There were no cases of reconversion to open surgery.

91% received amoxicillin/clavulanic acid as prophylactic or treatment antibiotic therapy according to our protocols and the rest of the patients adjusted to intraoperative findings with ceftriaxone or gentamicin together with metronidazole.

Regarding the main variables of our study, the hospital stay in the InA group was 3 days²⁻³ as well as in the DeA group³⁻⁴ ($p = 0.11$).

There was one case of complication in the whole series: a surgical wound infection in a patient with perforated appendicitis in the DeA group. However, as it was only one patient, the statistical analysis did not detect significant differences ($p = 1$).

Table 2 shows the results of the analysis for the secondary objective. A significant relationship was found in the subgroup of gangrenous appendicitis with the presence of fever, leukocytosis, PMN percentage, CRP, and the presence of appendicolith. Neither age nor sex, nor hours from symptoms onset to diagnosis (within our 24-hour cut-off), nor the number of hours from diagnosis to surgery were associated with a higher percentage of gangrenous appendicitis.

In multivariate logistic regression analysis adjusted with the variables appendicolith, hours from diagnosis to surgery, CRP, age, and sex, we found an independent association between the presence of appendicolith and gangrenous appendicitis. The presence of appendicolith increased the likelihood of gangrenous appendicitis 6-fold [OR = 6.36 (1.07-37.5); $p = 0.041$]. In addition, there was a trend towards an inverse, non-significant relationship between the hours elapsed from diagnosis to surgery and the possibility of gangrenous appendicitis. This variable behaves as a protective factor, i.e., the more hours from diagnosis to surgery (within our maximum of 24) the less gangrenous appendicitis, although this data does not reach statistical significance [OR 0.92 (0.83-1.01); $p = 0.079$] (Table 3).

Table 1. Baseline characteristics at diagnosis of uncomplicated acute appendicitis. Quantitative variables are expressed in median and inter-quartile range 25-75%. The qualitative ones are expressed in number and percentage

	Immediate appendectomy n = 21	Deferred appendectomy n = 24	p
Age (years)	10 (9-12)	11 (9-13)	0.2143
Gender	Boys / Girls	18 (75%)/6 (25%)	0.133
Symptoms			
Vomiting	13 (61.9%)	8 (33.3%)	0.076
F	4 (19%)	8 (33.3%)	0.329
Muscle defense	16 (76.2%)	18 (75%)	1
Blumberg	18 (85.7%)	19 (79.2%)	0.705
Hours since onset of symptoms	12 horas (12-24)	18 horas (12-24)	0.5692
Blood analysis			
Leukocytes (median)	14.410 u/mm ³ (13.100-16.260)	13.780 u/mm ³ (8.925-20.190)	0.7158
Polymorphonuclear (median %)	80% (65-82)	80.9% (71.9-86.5)	0.4946
CRP	3.7 mg/L (1.33-21.6)	13.1 mg/L (3.1-28.6)	0.1942
US scan findings			
Appendix diameter	8 mm (7-9)	7 mm (6.5-9)	0.1168
Appendicolith	4 (19%)	8 (33%)	0.329
Free liquid	9 (42.9%)	9 (37.5%)	0.727
Fat involvement	19 (90.5%)	20 (83.3%)	0.67

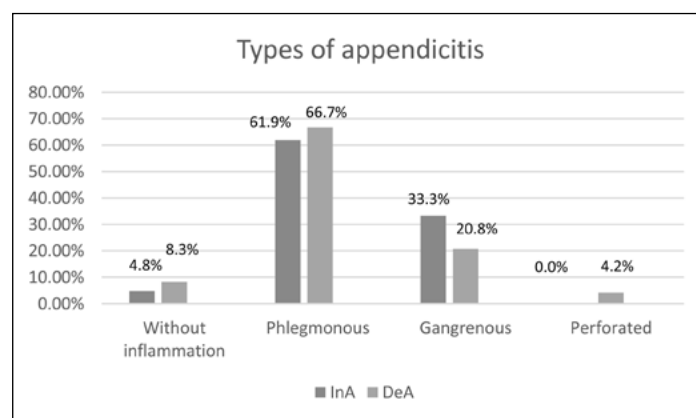


Figure 1. Distribution of the different types of appendicitis in percentage in the immediate group (InA) and in delayed appendectomy group (DeA)

Discussion

In children with uncomplicated acute appendicitis, our main finding was that deferred appendectomy did not increase hospital stay or postoperative complication rate.

The ideal timing of surgery in uncomplicated appendicitis is a matter of controversy, although patient characteristics and general condition prevail in decision-making¹⁶. In centers where pediatric surgery is not available 24 hours a day and if surgery cannot be

deferred, the following step is to refer the patient to another center. This results in an increase in the burden of care in these hospitals¹⁷. For the families, it also means a trip far from their homes, which makes it difficult to accompany the patient and generates a source of stress. Therefore, it is essential both to confirm the safety of deferred appendectomy and to correctly identify the patients in whom surgery could be safely delayed. This would avoid referrals and optimize resources while reducing stress for families.

Our center follows a strict protocol for deferred appendectomy in cases of clinical stability of the patient, with less than 24 hours from the onset of symptoms and without ultrasound data of complicated acute appendicitis (abscess, perforation, echogenic fluid). However, the presence of perforated appendicitis in the DeA group stands out in our data. This patient had the same characteristics as the rest of the children in the study: few hours of evolution, clinical stability, and no relevant data. In addition, he presented the complication of infection of the surgical wound. Our future efforts should be aimed at identifying patients who may have a more rapid progression of their condition, as occurred in this child, and who would not be susceptible to defer surgery¹².

Some studies postulate that a different immune response to infection would cause a more rapid progression to necrosis or perforation in some patients^{10,11}. In addition, the mechanical factor caused by the presence

Table 2. Univariate analysis of association with gangrenous appendicitis. The quantitative variables are expressed in median and interquartile range 25-75%. The qualitative ones are expressed in number and percentage

	Phlegmonous appendicitis	Gangrenous appendicitis	p
Age (years)	10 (8-13)	10 (9-12)	0.79
Gender (boys/girls)	65.6%/61.5%	34.4%/38.5%	0.528
Hours since onset of symptoms	24 (3-24)	16 (12-24)	0.979
Fever	6 (18.7%)	6 (46.1%)	0.076
Vomiting	14 (43.7%)	7 (53.85%)	0.743
Leukocytosis (u/mm ³)	8.290 (7.400-12.520)	13.900 (10.880-16.310)	0.016
Neutrophilia (%)	46.5% (42-80)	78.7% (65.8-83.2)	0.028
PCR	1 mg/l (0.9-1)	8.45 mg/l (2.24-15.7)	0.013
Appendicolith	5 (15.6%)	7 (53.8%)	0.022
Hours from diagnosis to surgery	21 (4-24)	17 (3.5-21)	0.183

Table 3. Final logistic regression model of association with gangrenous appendicitis.

Factor Predictor	Odds Ratio	95% confidence interval	p
Appendicolith	6.36	1.08 - 37.51	0.041
CRP	1.05	1.00 - 1.11	0.035
Hours from diagnosis to surgery	0.92	0.83 - 1.01	0.079

of appendicolith may generate greater intraluminal pressure on the appendix, favoring its earlier disruption¹⁸. These patients would therefore not be candidates for deferred surgery. A complementary analysis to respond to the secondary objectives was proposed due to the first results that showed an overall percentage of 28.9% of gangrenous appendicitis in the overall series (33.3% and 20.8% in each group), which seemed high considering that these were patients with less than 24 hours of evolution since the onset of symptoms, with no data of severity or clinical instability, and with exactly the same inclusion criteria in both groups.

Multivariate analysis showed a significant relationship with leukocytosis, left shift, and CRP. These data do not seem to be a cause but a consequence of a more advanced infection that manifests with more analytical alteration. The presence of appendicolith was also significantly associated with the gangrenous appendicitis group, which could be a causal element due to the mechanical effect mentioned above¹⁸.

We believe it is interesting to mention that the hours elapsed from the onset of symptoms to diagnosis were not related to the presence of more advanced appendicitis, which agrees with the theory that complicated appendicitis depends on other factors in addition to the time of evolution, whether mechanical, such as appendicolith, or immunological^{8,18}.

In the multivariate analysis, adjusting for the effect of the rest of the variables, we obtained an unexpected result, the hours until surgery would exert a protective effect, which is a trend in the opposite direction. A possible explanation for this tendency is that from the time of diagnosis until surgery, we are already doing a medical treatment of appendicitis with antibiotic therapy, intestinal rest, and rehydration. A subgroup of patients, due to the characteristics of their appendicitis or their immune profile, could respond to this medical treatment, which is already being evidenced in studies that propose the option of conservative management of uncomplicated acute appendicitis in both children and adults^{13,14}.

Our study has several limitations. The most important ones are related to the small sample size and the fact that group assignment was arbitrary and not random. However, our results are in line with systematic reviews and meta-analyses on the subject^{1,3} and seem interesting as a starting point for future research.

In conclusion, deferred appendectomy in cases of uncomplicated acute appendicitis in our series did not statistically significantly increase complications or postoperative length of hospital stay. The presence of appendicolith is associated with a higher probability of developed appendicitis, as well as increased leukocytosis, left shift, and elevated CRP. We believe that it

is essential to correctly identify patients susceptible to deferred treatment in order to avoid referrals to other centers and to prioritize surgery in patients with more risk factors for complications.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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