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ORIGINAL SCIENTIFIC REPORT

Delayed Surgery for Perforated Appendicitis is Feasible in Children Without Compromising the Outcome in Selected Cases

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Abstract

Background and aim The relationship between time to surgery and risk of postoperative complications and re-intervention has not been conclusively investigated in pediatric perforated appendicitis (PA). The aim of this study was to determine whether time to appendectomy (TTA) is a risk factor for postoperative complications and re-intervention in a cohort of children undergoing appendectomy for PA.

Methods A total of 254 children (age: 8.7 ± 3.7 years) undergoing appendectomy for PA were retrospectively evaluated and stratified into Group I–III according to the Clavien-Dindo classification for postoperative complications (Group I n = 218, 86%; Group II n = 7, 3%; Group III n = 29, 11%).

Results The TTA was comparable between all groups (group I: 8.8 ± 9.2 h; group II: 7.8 ± 5.3 h; group III: 9.5 ± 9.6 h; overall: 8.8 ± 9.1 h; p = 0.885). A C-reactive protein (CRP) value at admission of ≥128.6 mg/l indicated a higher risk for developing Grade II complications with no need for re-intervention (OR: 3.963; 95% CI: 1.810–8.678; p = 0.001) and Grade III complications with the need for re-intervention (OR: 3.346; 95% CI: 1.456–7.690; p = 0.004). This risk was independent of the TTA (OR: 1.007; 95% CI: 0.980–1.035; p = 0.613).

Conclusions Appendectomy can be delayed by an average time delay of about 9 h in children with PA without increasing the risk of postoperative complications and re-intervention, also in patients at high risk defined by the initial CRP level ≥ 128.6 mg/l. This data may support the correct risk-adjusted scheduling of surgical interventions in times of limited capacity.

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Introduction

In children and adolescents, appendicitis represents the most frequent indication for surgery [1]. Progression of appendix inflammation to perforated appendicitis [PA] occurs in about 20% of cases [2]. Postoperative complications and re-interventions rates are more frequent in PA, compared to non-perforated appendicitis [3, 4]. In a previous study, we reported a postoperative complication rate of 11.7% and a complication-related intervention rate of 10.4% for PA [2]. This leads to longer hospital stays and increased burden on both patients and the pediatric healthcare system [4–6]. Performing appendectomy before perforation might reduce the postoperative complication rate, but a correlation between time to appendectomy (TTA) and risk of perforation and postoperative morbidity has not been determined conclusively [7–10].

Clinical management of suspected pediatric appendicitis varies [1]. Some institutions postpone appendectomy until the next morning in children who present to the hospital during the night because there is no evidence that the time between in-patient admission and surgery affects the postoperative results [11]. Others consider suspected pediatric appendicitis an emergent surgical intervention [12], but capacity limitations might delay surgery.

The value of TTA in predicting the postoperative outcome in pediatric PA is not clear. Studies on pediatric PA have reported no correlation between TTA and surgical site infection rate [13, 14] or length of hospital stay [15]. In contrast, other studies have reported a positive correlation between length of stay and TTA [7]. In the present study, we investigated the correlation between TTA, postoperative complications and re-intervention rates in children with PA.

Material and methods

Study design

Medical records of all patients aged 18 years or younger diagnosed with PA at appendectomy in our university center for pediatric surgery from September 2007 to March 2019 were retrospectively analyzed. PA was defined at surgery by a visible hole in the appendix with or without the presence of stool in the abdomen[16]. The local ethical committee approved the study protocol. Due to the retrospective study design, patient's written study participation consent was waived in accordance with the local ethical committee.

Surgical procedure

Appendectomy was performed according to the surgeon's preference. Laparoscopic appendectomy was performed using three trocars (10-mm periumbilically, 5-mm trocar each right and left lower quadrants) and three endo-loop sutures. An abdominal incision in the right lower quadrant or a median laparotomy was performed for open appendectomy, and the appendicular stump was sutured. Stapling devices were not used.

Data collection

Pre-, intra-, and postoperative data were evaluated. Preoperative variables included patients' demographics, type, and duration of abdominal complaints prior to presentation to our clinic, fever (> 38.5 °C), tenderness or peritonitis, C-reactive protein (CRP), white blood cells count (WBC), and abdominal ultrasound results. Intraoperative variables included time of surgery and type of operative access. Variables included type and duration of preoperative and postoperative antibiotics, and laboratory values indicating inflammation (CRP and WBC) at discharge. The definition of postoperative complications was as follows: intraabdominal abscess (ultrasound or MRI showing a localized hypoechoic lesion), intestinal obstruction (mechanical interruption of intestinal passage requiring operative adhesiolysis), wound infection (healing deficit of the skin wound with infectious secretion), dehiscence of the abdominal fascia (healing deficit of the abdominal fascia with dehiscence), purulent peritonitis (pus in two or more abdominal quadrants). Follow-up duration was defined by the last presentation for appendicitis-related treatment at our clinic. Time from patient admission to appendectomy (TTA) was stratified as less than 3 h; more than 3 and less than 6 h; more than 6 and less than 12 h; more than 12 and less than 24 h; and more than 24 h.

Subgroup analysis

Patients were stratified according to the Clavien-Dindo classification of surgical complications into three groups [17]. Group I included patients with at most Clavien-Dindo Grade I complications: "Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside" [17]. Group II included patients with Clavien-Dindo Grade II complications: "Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood

Table 1 Patient demographics and findings at admission (Group I: Clavien-Dindo postoperative complications Grade I at most; Group II: Clavien-Dindo postoperative complications Grade II; Group III: Clavien-Dindo postoperative complications Grade III) [18]

	Groups				*p*-value			
	I	II	III	Total	All groups	I/II	I/III	II/III
Patients (*n*)	218 (86%)	7 (3%)	29 (11%)	254 (100%)				
Age (y)	8.6 ± 3.6	8.2 ± 4.9	10.1 ± 3.9	8.7 ± 3.7	0.116			
Sex (ratio m:f)	1.5:1	1:1.3	1.1:1	1.4:1	0.506			
BMI	17.2 ± 3.6	17.7 ± 3.8	18.6 ± 4.5	17.3 ± 3.7	0.147			
Length of complaints (d)	2.8 ± 2.7	4.5 ± 2.2	4.6 ± 3.8	3.0 ± 2.9	0.002	0.333	0.005	0.998
Body temperature (°C)	38.5 ± 0.8	38 ± 0.5	38.5 ± 0.9	38.5 ± 0.8	0.409			
Serum values								
CRP (mg/dl)	115.7 ± 85.0	174.0 ± 43.2	167.1 ± 75.6	123.1 ± 85.0	0.003	0.241	0.008	0.983
Leucocytes (/nl)	19.9 ± 22.8	25.5 ± 4.5	17.6 ± 7.2	19.8 ± 21.3	0.692			
Ultrasound								
Suspicion of PA	49 (22.8%)	4 (57.1%)	7 (24.1%)	60 (23.6%)	0.150			
Appendix								
Hyperperfused	20 (9.2%)	1 (14.3%)	0 (0.0%)	21 (8.3%)	0.183			
Diameter > 7 mm	81 (37.2%)	4 (57.1%)	8 (27.6%)	93 (36.6%)	0.248			
Free fluids	96 (44.0%)	2 (28.6%)	13 (44.8%)	111 (43.7%)	0.569			

transfusions and total parenteral nutrition are also included" [18]. Group III included patients with Clavien-Dindo Grade III complications: "Requiring surgical, endoscopic or radiological intervention. IIIa: Intervention not under general anesthesia. IIIb Intervention under general anesthesia" [17].

Data analysis

Categorical data, expressed as frequency distributions, were compared using a Chi-squared test. Continuous data, expressed as mean values ± standard deviation, were compared using a one-way ANOVA or a T test, as appropriate. If a significant difference was found using ANOVA, a post hoc comparison using the Scheffe test was performed. Odds ratios (OR) were calculated by binary logistic regression. A receiver operating characteristic (ROC) curve analysis was used to determine cut-off values for different parameter. A $p < 0.05$ was considered significant for all analyses. The statistical analysis software SPPS Version 25 (IBM, Armonk, NY, USA) was used for data analysis.

Results

Demographics and findings at admission

A total of 1244 children < 18 years of age underwent appendectomy for appendicitis during the study period. Of these patients, 254 children (20.41%) had PA and were included in this study (Table 1).

Time from admission to appendectomy and surgery data

The TTA was comparable between groups (group I: 8.8 ± 9.2 h; group II: 7.8 ± 5.3 h; group III: 9.5 ± 9.6 h; overall: 8.8 ± 9.1 h; $p = 0.885$). More than 80% of patients with postoperative complications and re-interventions underwent appendectomy within 12 h of admission (Table 2, Fig. 1).

Postoperative antibiotics and clinical course

Antibiotics were administered intraoperatively, after a smear test of intrabdominal fluids/appendix was collected, and continued postoperatively. Antibiotics were given intravenously as a combination of cefotaxime (100 mg/kg in three doses per day) and metronidazole (20 mg/kg in two doses per day). Clavien-Dindo grade II and III postoperative complications occurred in 33 (13%) patients in combination (Table 3). An occurring ileus ($n = 17$ cases) underwent reoperation in all cases (group III), an occurring wound infection ($n = 14$ cases) underwent reoperation in eight cases (group III), and an abdominal fascia dehiscence ($n = 8$) underwent reoperation in seven cases (group III) (Table 3).

Table 2 Time from admission to appendectomy (TAA) and surgery data, (Group I: Clavien-Dindo postoperative complications Grade I at most; Group II: Clavien-Dindo postoperative complications Grade II; Group III: Clavien-Dindo postoperative complications Grade III) [18]

	Groups				*p*-value			
	I	II	III	Total	All groups	I/II	I/III	II/III
Time from admission to surgery (h)	8.8 ± 9.2	7.8 ± 5.3	9.5 ± 9.6	8.8 ± 9.1	0.885			
< 3 h	22 (10.1%)	1 (14.3%)	2 (6.9%)	25 (9.8%)	0.966			
≥ 3 h, < 6 h	86 (39.4%)	2 (28.6%)	13 (44.8%)	101 (39.8%)	0.966			
≥ 6, < 12 h	73 (33.5%)	3 (42.9%)	9 (31.0%)	85 (33.5%)	0.966			
≥ 12, < 24 h	22 (10.1%)	1 (14.3%)	2 (6.9%)	25 (9.8%)	0.966			
> 24 h	15 (6.9%)	0 (0.0%)	3 (10.3%)	18 (7.1%)	0.966			
Surgical access								
Laparoscopic	133 (61.0%)	5 (71.4%)	16 (55.2%)	154 (60.6%)	0.699			
Open overall	85 (39.0%)	5 (71.4%)	15 (51.7%)	100 (39.4%)	0.699			
Intradominal findings								
Peritonitis								
Local	117 (53.7%)	5 (71.4%)	21 (72.4%)	143 (56.3%)	0.115			
All four quandrants	40 (18.3)	3 (42.9%)	9 (31.0%)	52 (20.5%)	0.093			
Purulent	187 (85.8%)	7 (100%)	23 (79.3%)	217 (85.4%)	0.352			
Operative time (h)	1.5 ± 0.6	1.7 ± 0.4	1.9 ± 1.2	1.5 ± 0.7	0.004	0.676	0.005	0.754

Predictors for complications and re-intervention

The CRP value at admission predicted occurring Clavien-Dindo Grade II postoperative complications requiring a re-intervention (AUC: 0.720 ± 0.042, 95% CI: 0.637–0.803, $p < 0.001$). The cut-off value of 131.4 mg/l showed a 71.4% sensitivity and a 65.1% specificity. The CRP value determined at admission was predictive of the postoperative complications requiring a re-intervention (Clavien-Dindo Grade III) with an AUC: 0.700 ± 0.048, 95% CI: 0.606–1.000, $p < 0.001$. The CRP-value cut-off of 128.6 mg/l showed a sensitivity of 69%, and a specificity of 66.1% (Fig. 2). Overall, 107 patients had an initial CRP value ≥ 128.6 mg/l: 5 patients (71.4%) in the group II group, 20 patients (69%) in the group III, and 82 patients (37.6%) in group I ($p = 0.001$). The odds-rations of patients with an initial CRP value of ≥ 128.6 mg/l for developing postoperative complications were group I: 0.252 (95%CI: 0.115–0.552, $p = 0.001$), group II: 3.963 (95%CI: 1.810–8.678, $p = 0.001$), and group III: 3.346 (95% CI: 1.456–7.690, $p = 0.004$). Patients with CRP values ≥ 128.6 mg/l at admission had a comparable TTA to patients with CRP values <128.6 mg/l at admission (9.2 ± 9.6 h vs. 8.6 ± 9.0 h, $p = 0.614$). This indicates that the risk predicted by CRP value at admission is independent of the TTA (OR: 1.007, 95% CI: 0.980–1.035, $p = 0.613$).

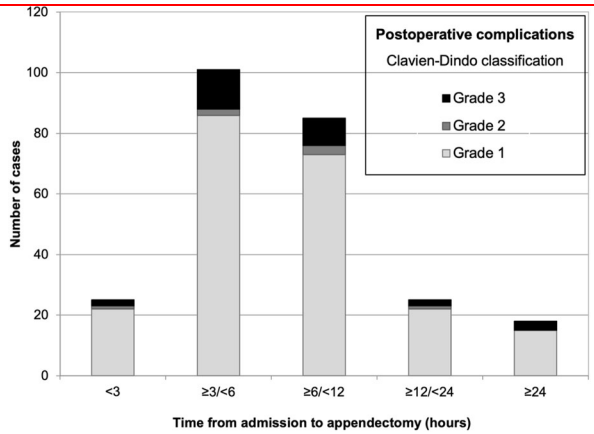

Fig. 1 Distribution of postoperative complications Grade I-III (according to Clavien-Dindo classification [17]) in relation to the time from admission to appendectomy

Discussion

Reducing the TTA in cases of suspected appendicitis is generally assumed to decrease the rate of perforation and morbidity. However, TTA has not been correlated to perforation rate in pediatric appendicitis [18, 19]. The reported rate of pediatric perforation within a 12-h TTA is about 35% and decreases to 10% after 24-h TTA [11]. One study

Table 3 Postoperative antibiotics and clinical course (Group I: Clavien-Dindo postoperative complications Grade I at most; Group II: Clavien-Dindo postoperative complications Grade II; Group III: Clavien-Dindo postoperative complications Grade III) [18]

	Groups				*p*-value			
	I	II	III	Total	All groups	I/II	I/III	II/III
Antibiotics i.v								
Preoperative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)				
Intra- and postoperative								
Cefotaxime (d)	6.7 ± 1.5	6.5 ± 2.1	8.8 ± 5.5	6.9 ± 2.4	< 0.001	0.984	< 0.001	0.097
Metronidazole (d)	5.1 ± 1.4	5.6 ± 1.4	7.6 ± 3.8	5.4 ± 2.0	< 0.001	0.813	< 0.001	0.040
Initial antibiotics not								
compliant to antibiogramm	40 (18.3%)	4 (57.1%)	10 (34.5%)	53 (20.9%)	0.276			
Postoperative complications								
Ileus	0 (0.0%)	0 (0.0%)	17 (58.6%)	17 (6.7%)	< 0.001			
Wound infection	0 (0.0%)	6 (85.7%)	8 (27.6%)	14 (5.9%)	< 0.001			
Abdominal fascia dehiscence	0 (0.0%)	1 (14.3%)	7 (24.1%)	8 (3.1%)	< 0.001			
Length of stationary stay (d)	9.8 ± 2.1	12.1 ± 2.9	16.5 ± 7.4	10.6 ± 3.8	< 0.001	0.164	< 0.001	0.005
Follow-up (d)	82.9 ± 23.7	215.6 ± 148.3	285.6 ± 106.2	130.7 ± 36.5	< 0.001	0.040	0.005	0.735

reported an increase in PA rate with an increasing TTA, but this was a non-significant trend [18]. Therefore, we cannot assume that surgery is urgently needed to avoid perforation, even though PA is associated with higher postoperative complications and re-intervention rates compared with non-perforated appendicitis in children [3, 4].

In the present study, we could show that a 9-h TTA had no effect on the risk for complications or re-interventions in pediatric PA. Over 40% of patients with complications and over 50% of patients requiring re-intervention underwent appendectomy within 6 h of admission. Complication and re-intervention rates fell to 0% and 7%, respectively, when appendectomy was performed > 24 h after admission. These findings dissent an association between longer TTA, increased complication and re-intervention rates. Our findings suggest that pediatric appendectomies can be delayed during periods of limited capacity without increasing the risk for the patients, even if perforation has

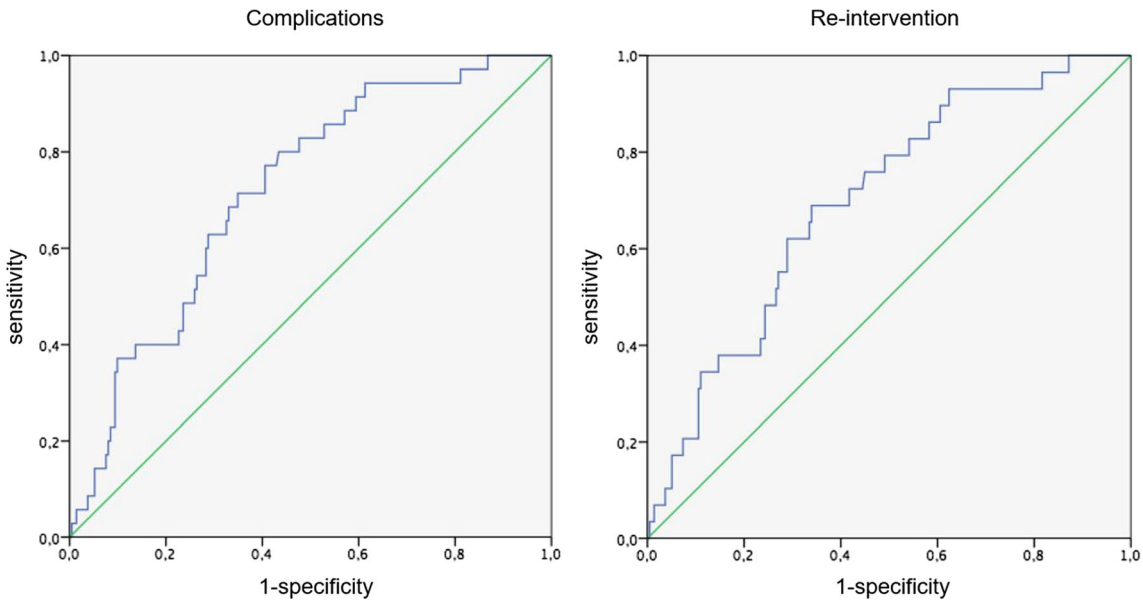

Fig. 2 ROC analysis for CRP values at admission as a predictor of postoperative complications

occurred. This confirms findings from previous studies that the TTA has no impact on the postoperative outcome in children undergoing appendectomy for appendicitis [9, 11, 15, 18, 20, 21]. However, these studies evaluated a mixed cohort of children with different degrees of appendicitis, and the number of PA cases was limited. The present study has added valuable information by evaluating the effect of TTA on postoperative outcome in children with PA. We have also confirmed our previous finding that the CRP value at admission can identify those children with pediatric appendicitis at high risk of postoperative complications and re-operations [2]. CRP values have also been reported to predict postoperative outcomes in adult patients [22]. In the present study, we showed that this CRP-defined high-risk group had a comparable TTA to the non-high-risk group. This might indicate that children with suspected appendicitis, presenting with a CRP value of $\geq$ 128.6 mg/l, and who are intraoperatively revealed to have PA, are at higher risk for complications and/or re-interventions following appendectomy; however, this risk is independent of the TTA. Of clinical importance, this implies that appendectomy can be delayed by on average 9 h, without increasing the risk for the patient and even in high-risk cases during times of limited clinical capacity. However, it should be noted that this subgroup is at higher-risk for complications. Hence, these patients might need a more intensive postoperative care to early prevent, detect, and address possibly developing complications. The indication for emergency surgery is an interdisciplinary decision based on different entities, including the patient's condition (e.g., if the patient is in a septic condition). However, in stable children not at high-risk, we believe that it is feasible to treat an appendectomy as an urgent, rather than an emergency intervention.

The present study did not confirm some risk factors for postoperative complications and prolonged stationary stay determined by others, including patient age [23], diarrhea or fever, WBC [3–5], duration of complaints [24], and BMI [5, 23, 25]. The latter could possibly be explained by the low average BMI (17.3 $\pm$ 3.7) measured in our study population. The ultrasound findings at admission were not useful for patient risk stratification in our cohort. Nevertheless, we consider abdominal ultrasound at admission as necessary to rule out other diagnoses. Our data highlight the limited predictive value of different preoperative clinical and sonographic parameters on the long-term outcome in children with PA undergoing appendectomy.

This study is limited by its retrospective nature and possible confounding bias. However, a prospective study comparing different TTAs in children with PA is not feasible for ethical reasons; therefore, retrospective studies provide the only data on which to base risk estimation. Strengths of this study include the clearly defined study group of children with a PA. In addition, the evaluated continuous variables were precise and easy to measure (TTA and CRP), in contrast to more subjective variables, such as abdominal muscular defense and indication for surgery. However, the TTA is dependent on multiple factors, including time to first evaluation, blood results, ultrasound findings, available operating theatre slots, and available personnel. Future studies are necessary to assess the effect of TTA reduction in the risk of postoperative complications and re-intervention.

In conclusion, the TTA in children with PA is not associated with an increased risk of postoperative complications and re-intervention. Children with suspected appendicitis presenting with a CRP value of $\geq$ 128.6 mg/l with a PA are at higher risk for complications and re-interventions following appendectomy. However, this risk is TTA-independent. Therefore, appendectomy can be delayed in pediatric patients with PA during periods of limited clinical capacity, without increasing the risk of postoperative complications and re-intervention, even in high-risk cases as defined high risk by the initial CRP value of $\geq$ 128.6 mg/l.

Author contributions Each of the authors substantially contributed to the study, fulfills the COPE requirements for authorship, and approved the manuscript in its' final version.

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Data availability This published article contains all analyzed data.

Declarations

Conflict of interest Authors have no conflict of interests to declare. No financial support was received for this article.

Ethical approval The local ethical committee approved the study protocol.

Informed consent Due to the retrospective nature of this study, no patient's informed consent was necessary.

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