

ORIGINAL ARTICLE

**Twenty-four hour versus Extended Antibiotic Administration
After Surgery in Complicated Appendicitis:
A Randomized Controlled Trial**

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The abstract is accepted as an oral presentation at the 77th Annual Meeting of the American Association for the Surgery of Trauma, September 2018 in San Diego, CA.

Background: Recent investigations noted noninferiority in short-course antimicrobial treatments following source control in abdominal infections. We set out to investigate noninferiority of a short and fixed (24-hour) antibiotic administration compared to extended treatment after source control in complicated appendicitis in a prospective single-center open-label randomized controlled trial.

Methods: After IRB approval, all consecutive adult patients (age ≥ 18 years) with complicated appendicitis including gangrenous appendicitis, perforated appendicitis, and appendicitis with periappendicular abscess between 5/2016 and 2/2018 were randomly allocated to antibacterial therapy limited to 24 hours (short) vs. >24 hours (extended) administration after appendectomy. Primary outcomes included composite postoperative complications and Comprehensive Complication Index (CCI). Secondary outcome was hospital length of stay (HLOS). Follow-up analysis at 1 month was conducted per intention and per protocol.

Results: A total of 80 patients were enrolled with 39 and 41 cases allocated to the short and the extended therapy group, respectively. Demographic profile and disease severity was similar between the study groups. Overall rate of complications was 17.9% and 29.3% in the short and extended group, respectively ($p=0.23$). Mean CCI did not differ between the study groups ($p=0.29$). HLOS was significantly reduced in the short therapy group (61 ± 34 vs. 81 ± 40 hours, $p=0.005$).

Conclusions: In the current prospective randomized investigation, the short (24-hours) antibiotic administration following appendectomy did not result in a worse primary outcome in complicated appendicitis. The short interval administration resulted in a significant reduction in HLOS with a major cost-saving and antibacterial stewardship perspective.

Level of Evidence: Level II, Randomized Controlled Trial

BACKGROUND

Appropriate perioperative antimicrobial administration is a basic tenet in gastrointestinal surgery to prevent surgical site infections (SSI) [1]. In non-complicated appendicitis including catarrhal or phlegmonous appendicitis, antimicrobial therapy following surgery is not indicated and may result in higher incidence of adverse events [2, 3]. However, in complicated appendicitis including gangrenous appendicitis, perforated appendicitis, or appendicitis with periappendicular abscess, antibiotic administration is recommended following source control in a minimum of 3-5 days according to the recent evidence-based guideline [4]. Similar to investigations that observed noninferiority of abbreviated antimicrobial therapy in abdominal infections overall, a recent prospective investigation suggested that a three-day antimicrobial administration following appendectomy in complicated appendicitis was noninferior to a five-day therapy [5- 7]. Furthermore, another small retrospective investigation by Kimbrell et al. observed that 24-hour antibiotic therapy was noninferior to extended administration in complicated appendicitis [8]. Based on the safety of the previous data on abbreviated antimicrobial therapy in these instances, we set out to investigate noninferiority of a short and fixed (24-hour), versus extended postoperative antimicrobial treatment after surgical source control in complicated appendicitis in a prospective open-labeled randomized controlled trial. We hypothesized that complication rates are similar between the study groups.

METHODS

After IRB approval, all consecutive patients with an age 18 year or older with acute appendicitis based on clinical diagnosis supported by laboratory markers, ultrasound and/or computed tomography per treating physician were eligible for enrollment and were consented prior to appendectomy for postoperative randomization when complicated appendicitis was encountered at surgery between 5/2016 and 2/2018. Randomization to intravenous antibacterial therapy limited to 24 hours (short) vs. >24 hours (extended) administration after appendectomy was performed with a computerized software within 24-hour period following surgery when both study groups received intravenous antimicrobial treatment per the study protocol. In patients allocated to short treatment, the antibiotic administration was terminated at 24 hours

after surgery and those allocated to extended treatment interval were managed at the discretion of the treating physician. Per the study protocol, likewise, the treating physician was allowed to extend the antibiotic treatment when clinically indicated in the short-treatment group. Appendicitis disease severity was classified using the disease severity score (DSS) dividing acute appendicitis into five grades: grade 1, inflamed; grade 2, gangrenous; grade 3, perforated with localized free fluid; grade 4, perforated with a regional abscess; and grade 5, perforated with diffuse peritonitis [9]. For randomization we included grade 2, 3 and 4 constituting an entity of complicated appendicitis. The DSS grade was assessed during appendectomy by surgeon performing the operation per the DSS grading protocol. Exclusion criteria included age <18 years, pregnancy, cognitive impairment, diabetes, immunodeficiency (primary or secondary), ongoing chemo- or radiotherapy for any oncological disease, radical treatment of a oncological disease within 5 years, penicillin allergy, presence of a mechanical heart valve or a synthetic vascular implants or grafts. Also, patients with grade 1 or grade 5 appendicitis per DSS were excluded.

Only aminopenicillins (amoxicillin with clavulanic acid or ampicillin with sulbactam) were administered. Antibiotic therapy was administered intravenously only in the short treatment group and in the extended group the intravenous administration was provided in 48 hours followed by a continued intravenous or an oral administration per treating physicians assessment. The decision for the length of antibiotic therapy in the extended therapy group was also made by a treating physician. The dosage of intravenous amoxicillin/clavulanic acid and ampicillin/sulbactam was 1.2g and 3 grams every 8 hours, respectively.

Data collection included demographics, laboratory markers (white blood cell count and C-reactive protein), antibiotic therapy, surgical treatment, complications per Clavien-Dindo (CD), Comprehensive Complication Index (CCI), and hospital length of stay (HLOS). CCI is a postoperative morbidity assessment scale based on CD classification, however, while CD classification includes only one most severe complication, the CCI includes all complications in a scale ranging from 0 (no complications) to 100 (complication resulting in patient's demise) [10, 11]. Higher CCI score depicts higher burden of complications.

Follow-up phone-call survey was performed 30 days after appendectomy and all the readmissions were documented. When patient indicated any adverse event on the phone-call survey, the adverse event and the respective treatment was confirmed in

the Estonian National Health Information System records containing health data submitted from all national hospitals and general practitioners.

Surgical site infection (SSI) including superficial and deep incisional and organ/space SSI (intra-abdominal abscess) was defined per Centers for Disease Control and Prevention (CDC) guideline [12].

Primary outcomes were post-operative complications per CD and CCI. Secondary outcome was HLOS.

The outcome analysis was performed per intention to treat (ITT) and per protocol (PP) follow-up. The *p*-values for continuous variables were derived from the Student *t* test or Mann-Whitney tests and for categorical values Chi-square or 2-sided Fisher's test were used. *P*-values <0.05 were considered statistically significant. Values are reported as a percentage for categorical variables and as mean \pm standard deviation (SD) for continuous variables. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Mac©) version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

During the study period, a total of 80 patients were enrolled with 39 and 41 cases in the short and the extended therapy group, respectively (Fig. 1). The average length of antibiotic therapy in the extended group was 6 ± 3 days. Thirty-day follow-up by phone-call survey was available in all patients. All demographic and laboratory variables were similar between the study groups depicted in the Table 1.

Table 2 demonstrates surgical interventions and classification of appendicitis per DSS assessed during appendectomy. Majority of the cases had laparoscopic appendectomy with similar rates in both study groups per ITT and PP analyses. Overall, grade 2, 3 and 4 appendicitis per DSS constituted 66.3%, 21.3% and 12.5% of the cases, respectively, and did not differ significantly between the study groups.

HLOS, detailed description of surgical complications per CD and CCI are listed in Table 3. HLOS was significantly reduced in the short therapy group (61 ± 34 vs. 81 ± 40 hrs, $p=0.005$ per ITT and 51 ± 21 vs. 81 ± 40 hrs, $p<0.001$ per PP analysis). Mean CCI and complication rate per CD did not differ significantly between the study groups and the respective follow-up analyses. Grade II complications predominated in both study groups. None of the patients had higher than grade IIIa complication. No mortalities were encountered.

Allocation to the short treatment group was violated in 7 cases (17.9%) where antibiotic therapy was extended by the treating physician. The most frequent causes for protocol violation were persistent fever in 5 patients and elevated postoperative C-reactive protein (CRP >250 mg/L) in two patients after 24-hours of antibiotic treatment. None of the patients had complications during the 30-day follow-up. Thus, per protocol analysis included 32 patients in the short interval group and 41 in the extended interval group, respectively.

Overall, superficial and deep SSIs occurred in 12.8% (n=5) and 7.3% (n=3) in the short and extended treatment groups, respectively ($p=0.54$). Organ/space SSI rate was likewise similar, at 7.7% (n=3) and 7.3% (n=3) in the 24-hour and extended treatment group, respectively ($p=0.71$). No difference in SSI was noted per ITT and PP analyses. Postoperative diarrhea occurred only in one patient in the extended treatment group with a negative *Clostridium difficile* PCR test.

The overall readmission rates were similar at 7.7% (n=3) and 7.3% (n=3) in fixed and extended treatment groups, respectively ($p=1.00$). Readmissions did not differ in ITT and PP analyses. Organ/space SSIs caused all rehospitalizations and interventions included percutaneous drain placement in three and antimicrobial therapy in three patients (Table 4).

DISCUSSION

The current prospective randomized controlled trial proved our hypothesis of noninferiority of a short and fixed, 24-hour therapy, compared to an extended treatment with antibiotics after source control in complicated appendicitis. Likewise, the study demonstrated significantly reduced hospital length of stay in the short therapy group providing a significant cost-saving perspective and an antimicrobial stewardship potential in patients suffering a common surgical emergency, i.e. complicated acute appendicitis.

The interval of postoperative antimicrobial therapy is a subject of a lively debate; however, multiple well-designed recent investigations have observed noninferiority in mixed groups of patients with intraabdominal infections [5, 6]. Nevertheless, prospective randomized studies specific to complicated appendicitis are scarce. According to the recent evidence, postoperative antimicrobial therapy in non-complicated appendicitis is not recommended and may result in worse outcomes including higher rate of *Clostridium difficile* infections and urinary tract infections

[2]. Also, HLOS and cost of care is significantly increased with the inappropriate administration of antimicrobials following surgery [2, 13]. Nevertheless, postoperative administration is indicated per the guidelines in complicated appendicitis, however, randomized controlled trials are lacking to guide the best practice [4]. A large prospective observational study by van Rossem et al. comparing three-day antibiotic treatment with five-day therapy in complicated appendicitis observed no benefit on infectious complications in extended administration [7]. Also, a small retrospective study by Kimbrell et al. reported similar rate of postoperative abscess incidence among patients receiving antibiotics for 24 hours or less compared to extended administration after appendectomy for complicated appendicitis, however, the number of patients included in the study was limited to only 8 patients in the 24-hour subgroup [8].

The current investigation allocating randomly patients to receive antibiotics per fixed 24-hour interval vs. extended interval observed no difference in the rate of post-operative complications or readmissions. Time from onset of symptoms to surgery and in-hospital delay being a known independent risk factors for post-operative complications were, likewise, similar [14-16]. The only significantly different outcome across all analyses was the HLOS with a significant global cost saving perspective. Also, antibiotics utilized in the current study are rather inexpensive and widely available providing opportunities for a wide implementation of our results. Our analysis included both intention to treat and per protocol follow-up with no significant difference in outcomes. The short therapy group treatment was violated per treating physicians in seven cases with most frequent cause being fever, however, none of the patients developed complications. A fever in the postoperative period is a common entity and may be related with non-infectious etiology including respiratory complications, drug fever, endocrine abnormalities or surgical insult with no indications for antimicrobial therapy [17].

The ITT analysis including all patients allocated to the respective study arms resulted in no differences in primary outcomes. The PP analysis excluded 7 patients (17.2%) from the short therapy group outcome analyses due to treating physicians' extension of the antibiotic therapy. Similar to many clinical trials, treating physicians rely on previously established clinical practices involving extended therapy in complicated appendicitis. The 7 cases subjected to extended therapy were excluded from the PP analysis resulting, however, in no significant differences in primary outcomes. The

secondary outcome, i.e. HLOS was significantly abbreviated in both follow-up analyses among patients allocated to the short therapy group.

The current study is limited by a low number of patients and inclusion of adult patients only. Nevertheless, to the best of our knowledge this is the very first randomized study to compare postoperative short antimicrobial therapy interval with extended treatment in complicated appendicitis. Thus, our study has a potential to modify postoperative management of acute complicated appendicitis in the era of rising antimicrobial resistance and to initiate large multi-center investigations to confirm our findings.

CONCLUSION

In the current prospective randomized investigation, the short (24-hour) antibiotic administration following appendectomy did not result in a worse primary outcome in complicated appendicitis. The short interval administration resulted in a significant reduction in HLOS with a major cost-saving and antibacterial stewardship perspective.

AUTHOR CONTRIBUTION

Sten Saar MD: literature search, study design, data collection, data analysis, data interpretation, writing, critical revision

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Table 1. Demographic profile and laboratory values of all patients

	Intention to treat			Per protocol		
	Short	Extended	<i>p</i> -value	Short	Extended	<i>p</i> -value
n	n=39	n=41		n=32	n=41	
Age (years)	44.2 ± 15.2	45.8 ± 15.3	0.627	42.8 ± 14.4	45.8 ± 15.3	0.384
Gender (male)	56.4%	63.4%	0.523	59.4%	63.4%	0.913
Charlson's co-morbidity index > 0	38.5%	39.0%	0.959	34.4%	39.0%	0.870
Time from onset of symptoms to surgery (hrs)	43.2 ± 31.2	48.4 ± 44.3	0.832	45.2 ± 32.8	48.4 ± 44.3	0.623
Time from ED admission to surgery (hrs)	9.7 ± 6.9	9.1 ± 5.1	0.675	10.3 ± 7.2	9.1 ± 5.1	0.446
Mean admission WBC x 10 ⁹ /L	14.7 ± 4.4	14.3 ± 3.7	0.641	14.4 ± 4.5	14.3 ± 3.7	0.901
Mean admission CRP mg/L	92 ± 99	87 ± 101	0.829	82 ± 93	87 ± 101	0.408

Abbreviations: ED, Emergency Department; WBC, white blood cell count; CRP, C-reactive protein

Table 2. Surgical interventions and classification of appendicitis severity per Disease Severity Score (DSS) of all patients

	Intention to treat			Per protocol		
	Short	Extended	<i>p</i> -value	Short	Extended	<i>p</i> -value
n	n=39	n=41		n=32	n=41	
Laparoscopic appendectomy	89.7%	95.1%	0.426	87.5%	95.1%	0.455
Open appendectomy	10.3%	4.9%	0.426	12.5%	4.9%	0.394
Conversion to open appendectomy	2.6%	0	0.488	3.1%	0	0.438
Length of operation (min)	52 ± 19	54 ± 20	0.680	51 ± 19	54 ± 20	0.433
DSS grade 2	71.8%	61.0%	0.306	75.0%	61.0%	0.310
DSS grade 3	20.5%	22.0%	0.875	15.6%	22.0%	0.561
DSS grade 4	7.7%	17.1%	0.313	9.4%	17.1%	0.499

Abbreviations: DSS, Disease Severity Score

Table 3. Hospital length of stay, complications per Clavien-Dindo classification and Comprehensive Complication Index of all patients

n	Intention to treat			Per protocol		
	Short n=39	Extended n=41	p-value	Short n=32	Extended n=41	p-value
HLOS (hrs)	61 ± 34	81 ± 40	0.005	51 ± 21	81 ± 40	<0.001
Any CD complication	17.9%	29.3%	0.234	21.9%	29.3%	0.475
Grade I per CD	2.6%	9.8%	0.360	3.1%	9.8%	0.377
Grade II	10.3%	14.6%	0.738	12.5%	14.6%	1.000
Grade IIIa	5.1%	4.9%	1.000	6.3%	4.9%	1.000
Grade IIIb-V	0	0	-	0	0	-
Mean CCI	3.93 ± 8.93	5.46 ± 9.57	0.298	4.79 ± 9.67	5.46 ± 9.57	0.579
Readmitted patients	7.7%	7.3%	1.000	9.4%	7.3%	1.000

Abbreviations: HLOS, Hospital Length of Stay; CD, Clavien-Dindo; CCI, Comprehensive Complication Index

Table 4. Interventions in all readmitted patients

	Intention to treat			Per protocol		
	Short	Extended	<i>p</i> -value	Short	Extended	<i>p</i> -value
n	n=39	n=41		n=32	n=41	
Antimicrobial therapy	2.6% (1)	2.4% (1)	1.000	3.1% (1)	2.4% (1)	1.000
Percutaneous drainage + antimicrobial therapy	5.1% (2)	4.9% (2)	1.000	6.3% (2)	4.9% (2)	1.000

Figure 1. Flowchart of all included patients

Abbreviations: DSS, Disease Severity Score; ITT, Intention to Treat; PP, Per Protocol

