The Suitability and Efficacy of Perioperative Antibiotics in Relation with the Surgical Wound after Appendectomy

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***Abstract*—There is no research currently exist about the use of ceftriaxone as perioverative antibiotics for appendicitis patient in Haji General Hospital Surabaya, so its relationship with the surgical wound after appendectomy is remain unknown. This research is conducted to determine the suitability and efficacy of ceftriaxone, also to identify other factors that influence the surgical wound. This was a prospective cohort study of 25 patients (age ≥ 15 years old) between June–August 2015. The specimens culture demonstrated that 12 bacteria were E. coli, 1 ESBL-producing E. coli and 12 negative. Antibiotics susceptibility testing showed that 41,67% E. coli was susceptible to ceftriaxone. There was no significant relationship between suitability of postoperative antibiotics and surgical wound after appendectomy in non-perforated cases (p=0,505), while perforated case defined a significant relationship (p=0,011). The factors which significantly related with surgical wound were gender (p=0,014) and duration of surgery (p=0,017). Ceftriaxone was still effective as perioperative antibiotics. Postoperative antibiotics were only required for perforated appendicitis, whereas prophylactic antibiotic was known to be adequate in the case of non-perforated.**

***Index Terms*—suitability, efficacy, antibiotic, surgical wound, appendectomy**

I. Introduction

Appendectomy is the gold standard therapy in appendicitis and classified as clean contaminated surgery. This procedure requires prophylactic antibiotics to prevent infections that can occur during or after surgery. Incidence of Surgical Site Infection (SSI) after appendectomy was 12,2%, where incidence of SSI in perforated appendicitis 4 to 5 times higher than non-perforated [1], [2].

The incidence of SSI after appendectomy can be reduced between 1-5% with prophylactic antibiotics. [3] Selection of antibiotic prophylaxis depends on the type of surgery, infection-causing bacteria, and the pattern of bacterial susceptibility to antibiotics at local hospital where the surgery performed. [4]-[6] Although there was already a general guideline for the use of antibiotics and some studies that can be used as a reference in the selection of antibiotics in appendectomy, but the data about the factors that affect SSI, the pattern of bacterial that cause appendicitis and it susceptibilities to antibiotics in a hospital still needed because it can be different for each hospital.

Based on these reasons, this research was conducted to determine the relationship between suitability and efficacy of ceftriaxone as perioperative antibiotic, also to identify other factors that influence the surgical wound after appendectomy.

II. Methods

This prospective cohort study was performed at Haji General Hospital Surabaya, one of government hospital, since June until August 2015. Data was collected from 25 patients who were diagnosed to have acute, chronic or perforated appendicitis (age ≥ 15 years). Bacterial profile was isolated from appendices specimen in patients undergoing appendectomy.

All patients received 2 grams of ceftriaxone as prophylactic antibiotic (30-60 minutes before incision). After the surgery, patients received 1 grams of ceftriaxone twice times daily as postoperative antibiotic.

The suitability of antibiotics compared to the result of culture and susceptibility testing from clinical microbiology laboratories. According to the results, if it show that bacterial were resistant to ceftriaxone, then ceftriaxone will be replaced by surgeon with other susceptible antibiotics.

Efficacy of antibiotic in relation with surgical wounds was observed at day 8 after appendectomy by using Southampton Wound Scoring System. Observation also performed in outpatient department for patients who discharge before day 8. Those patients who lost to follow-up were excluded. Data were analysed by using SPSS statistic for windows, version 20. The p-value of < 0,05 was considered as statistically significant.

This study was approved by the ethical committee of Haji General Hospital Surabaya. Patients had been given a description of the research procedures and had signed the statement of consent form.

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III. Results and Discussion

A. Recruitment Profile and Clinical Characteristic

During the research period, 28 patients with clinical diagnosis appendicitis undergoing open appendectomy were considered to be involved in this research. One patient was excluded because it failed to obtain a specimen of appendix and two patients were lost to follow-up in outpatient department. Patients who completed the entire procedure was 25. Recruitment profile of patient is ilustrated in Fig. 1, while the characteristics of the patients are listed in Table I.

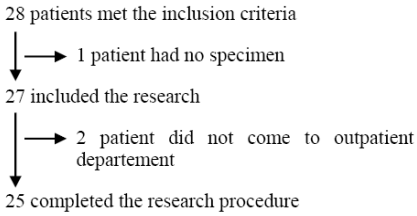

Figure 1. Recruitment profile

Based on Table I, majority patient in this research were male (64%). The same pattern can also be seen in other studies [7], [8]. Appendicitis most common in the age of 15-25 years. This is consistent with one of aetiology of appendicitis that lymphoid hiperplasia, because lymphoid tissues at that age is very abundant. There were 11 patients with perforated appendicitis (81,81% male), these result is similar to previous study which also showed that the incidence of perforated appendicitis more frequently in male [9].

TABLE I. Characteristics of the Patients

Characteristic	Number	%
Gender		
Male	16	64
Female	9	36
Diagnosis		
Non Perforated	14	48
Perforated	11	52
Classification of surgery		
Clean contaminated	21	84
Contaminated	1	4
Dirty	3	12
Type of surgery		
Elective	6	24
Urgent	7	28
Emergency	12	48
Duration of surgery		
≤ 1 hour	7	28
> 1 hour - ≤ 2 hour	18	72
Age		
15-25 years	14	56
26-35 years	1	4
36-45 years	5	20
46-55 years	2	8
> 55 years	3	12

B. Bacterial Profile

Identification of the bacteria that causes appendicitis is conducted to determine any bacterial profile associated with the emergence of the disease. All results of specimens culture showed the bacteria that cause appendicitis were *Escherichia coli* (E. coli), one of them was Extended Spectrum Beta Lactamase (ESBL). Meanwhile, 12 specimens did not show any bacterial growth or negative. Percentage of each bacterial are listed in Table II. This result is similar to previous study, thus indicating that E. coli (gram-negative bacterial) are the most responsible for the occurrence of appendicitis [10].

TABLE II. Result of Specimens Culture

Bacterial	Number	%
Escherichia coli	12	48
ESBL-producing E. coli	1	4
Negative	12	48

E. coli was estimated to be most common cause of appendicitis because one of normal flora in the gut. In addition, the nature of the E. coli bacteria that can perform fast proliferation and able to penetrate the tissue surface also support these bacteria to cause inflammation of the appendix. Bacterial adhesion to epithelial cells was the first step of the infection process, followed by the invasion and the emergence of damage to the appendix. E. coli was able to perform all of these processes with several virulence factors, which are haste-cell-surface-modifying factors, toxins, hemolysin and cytotoxin necroting factor type 1 [10], [11].

Inflammation caused by bacteria was associated with the main cause of appendicitis that is obstruction. Lymphoid hyperplasia and faecolith which causes obstruction of the appendix was the first step that cause normal flora in intestinal overgrowth which then lead to increased intra-luminal pressure and inhibits blood flow to the appendix so that the appendix was become congested and ischemia. Immediately followed by translocation and infection by the bacteria that ultimately makes inflammation [10]. The combination between obstruction and inflammation make appendectomy and perioperative antibiotic therapy remains became the gold standard in the treatment of appendicitis [1].

The majority negative specimens were specimens of nonperforated appendicitis cases. From 12 specimens, 66 67% of culture results showed no bacterial growth.

In addition, 3 of 4 patients that showed positive culture results, has been discharged from the hospital before the results were obtained. So it can not be adjusted for the suitable antibiotic susceptibility testing. Although antibiotics are used by these patients was not suitable (intermediet or resistant), but all patients in a stable condition and did not had surgical site infection.

This result was similar to previous study in Nottingham. The study showed that 60.5% of the culture did not show any bacterial growth. And 42.7% patients are already discharge of the hospital before culture results obtained, so that the culture results become less useful. This study suggests a culture routine should only be done in cases of perforated appendicitis and for patients with extreme ages (<10 or> 50 years) [12]. So it seemed that culture routine and postoperative antibiotics should not be given in patients with nonperforated appendicitis.

C. Antibiotic Susceptibility Testing

Antibiotic susceptibility testing was collected to see the pattern of antibiotics that are still effective and can be

recommended as perioperative antibiotics in patients with appendicities, foremost in Haji General Hospital. Results of antibiotic susceptibility testing showed that E. coli had 100% susceptibility to meropenem, cefoxitin and fosfomycin; 91,67% susceptibility to piperacillin-tazobactam; 66,67% susceptibility to gentamicin; 58,33% susceptibility to amikacin, cefepime, aztreonam and levofloxacin; 50% susceptibility to cefixime, ceftazidime, ampicillin-sulbactam and ciprofloxacin; 41,67% susceptibility to ceftriaxone, amoxicillin-clavulanat and chloramphenicol; 33,33% susceptibility to cotrimoxazole and tetracyclin. Cefotaxime and cefuroxime were no longer recommended because the susceptibility of E. coli only 16,67%. In this study, cefazolin and ampicillin were highly not recommended because 100% E.coli resistant to those antibiotics.

There was 1 ESBL-producing E. coli that cause perforated appendicitis. This bacteria only susceptible to amikacin, piperacillin-tazobactam, meropenem, cefoxitin and fosfomycin. Although it has been many years since it was first discovered in 1983, ESBL-producing bacteria was known as a bacteria that capable of producing the new class of enzyme β-lactamase. These bacteria are capable to hydrolyzing oxyimino groups making them survived from β-lactam antibiotics except carbapenem and cephamycin. Frequently, these bacteria are also capable of encoding plasmid and acquire resistance properties through the process of mutation that causes aminoglycoside and quinolone ineffective. The majority of ESBL-producing bacteria are multidrug resistant, so the choice of therapies to treat diseases caused by bacteria of this group is became restricted [13].

E. coli resistance to antibiotics can occur by several mechanisms. To fight the group of penicillin, sefalosforin and carbapenem, E. coli produces enzymes that capable to hydrolyzing the β-lactam ring, which are enzyme β-lactamase, ESBL and serine-carbapenemase [14]. β-lactamase is an enzyme that is clinically very important, produced by gram negative bacteria such as E. coli, and encoded by chromosome and plasmid. Genes encoding β-lactamase is transferred through a transposon, but it can also be a one integron composition. β-lactamase is able to hydrolyze almost all β-lactam class of antibiotics that has ester and amide bond in the structure, such as penicillin, sefalosforin, monobactam and carbapenem. This process can be inhibited by β-lactamase inhibitor, such as clavulanic acid, sulbactam or tazobaktam [15], [16]. This mechanism also explains the high sensitivity of E. coli to antibiotics piperacillin-tazobactam.

In this case, the patients was initially receiving ceftriaxone as antibiotic prophylaxis and postoperative, But after received the results of culture and susceptibility testing, surgeon directly replace ceftriaxone with meropenem because the result showed that the bacteria is resistant to ceftriaxone. This was similar to a case report of perforated appendicitis caused by ESBL-producing E. coli in Japan, which concludes that beside appendectomy and abcess drainage, suggested therapy with carbapenem class of antibiotics such as meropenem for 2 weeks to overcome abscess and prevent the emergence of other bacteria which are multidrug-resistant [13].

Meropenem is abactericidal antibiotic. This antibiotic has a high affinity to bind with high molecular weight penicillins-binding protein (PBP) that makes bacterial lysis and death. Meropenem's target on E. coli was on PBP 2 and PBP 3. The advantages of meropenem are able to withstand the process of hydrolysis by β-lactamase and mutation-mediated plasmid or bacterial chromosome. Furthermore, meropenem was not affected by the strains of Enterobacteriaceae producing plasmid-mediated β-lactamase SHV and TEM, the Extended-spectrum β-lactamase (ESBL), which is able to hydrolyze sefalosforin third generation antibiotics. Therefore, meropenem was the right choice in cases of appendicitis caused by ESBL-producing E. coli [17].

D. Relationship between Suitability and Efficacy of Antibiotics in Relation with Surgical Wound

Relationship between suitability and efficacy of antibiotics can only be performed on postoperative antibiotics due to limited variable of prophylactic antibiotics. We used the statistical correlation between suitability of postoperative antibiotics and surgical wound grading. There was no significant relationship between suitability of postoperative antibiotics and surgical wound after appendectomy in non-perforated cases (p=0,505), while perforated case defined a significant relationship (p=0,011). It showed that postoperative antibiotics were only required for perforated appendicitis, whereas prophylactic antibiotic was known to be adequate in the case of non-perforated.

The use of postoperative antibiotics was no longer recommended by guidelines and some studies. Guidelines by the Surgical Infection Society and the Infectious Disease Society of America about the diagnosis and management of complications of intra-abdominal infections in adults and children mentioned that in the case of acute appendicitis without perforation, abscess or peritonitis, only required narrow spectrum antibiotics prophylaxis and should be discontinued within 24 hours [18].

Therefore it was recommended for cases of non-perforated appendicitis without complications not need to provide postoperative antibiotic, since prophylactic antibiotics was adequate to reduce the risk of surgical site infection after appendectomy. Very important if it can be applied in Haji General Hospital Surabaya, because it can reduce the use of antibiotics which were not necessary, reducing the risk of complications that may occur from the use of antibiotics (antibiotic-related complication), such as antibiotic-associated diarrhea, decrease the risk of the spread of bacterial resistance to antibiotics and decrease antibiotic-associated economic burden for both patients and hospitals.

E. Factors that Influence the Surgical Wounds after Appendectomy

The following factors were analyzed by using statistical correlation to identify the relationship with surgical wound: classification of surgery, type of surgery,

diagnosis, duration of surgery, age, gender and body mass index. The factors which significantly related with surgical wound were gender and duration of surgery. Summary of the correlation test results are list in Table III.

TABLE III. RESULT OF CORRELATION TEST

No	Factors	P value
1	Duration of surgery	p =0,017
2	Gender	p =0,014
3	Type of surgery	p =0,210
4	Diagnosis	p =0,478
5	Age	p =0,672
6	Body Mass Index	p =0,696

This was consistent with the results of a cohort study in Thailand that assessing the risk of surgical site infection in patients appendectomy. According to the study, gender and duration of the operation was also a factor for the increased risk of surgical site infection after appendectomy. whereas other factors that also affect the increased risk of surgical site infections was the duration of antibiotic prophylaxis, age, increasing the American Society of Anaesthesiologists (ASA) score, length of hospitalization before surgery, emergency surgery and the type of operator skill differences [19].

F. Study Strengths and Weaknesses

The strengths of this study is this was the first prospective cohort study about perioperative antibiotics in appendicitis patients who underwent appendectomy in Haji General Hospital of Surabaya and we were able to get an overview of the susceptibility pattern of the bacteria that cause appendicitis to some antibiotics.

The study limitation was its a small sample size, although this sample already meet the minimum number of samples but if we earned more samples, the results of the research will be able to describe the real situation in the population of appendicitis patient.

IV. CONCLUSION

Ceftriaxone was still effective as perioperative antibiotics. Postoperative antibiotics were only required for perforated appendicitis, whereas prophylactic antibiotic was known to be adequate in the case of non-perforated.

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