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# Pentoxifylline as an Adjuvant Treatment of Perforated Acute Appendicitis in Relation to Surgical Site Infection in Children

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***Abstract:*** *In animal models and human trial, pentoxifylline has shown a beneficial pharmacological effect in the treatment of serious infective condition. It increases the inheritentfibrinolytic activity of the peritoneum and it reduces the fibrinogen levels, resulting in reduction of fibrin deposition, inhibition of formation as well as expansion of fibrin clots, thus preventing entrapment of bacteria in fibrin and accelerated bacterial clearance by preventing thrombosis of subperitoneal lymphatic. Other beneficial effect include improvement in microcirculation, increased bactericidal effect of chemotherapeutic agents by improve microcirculation, increased transmembrane permeability into bacterial cell. A prospective, placebo controlled trial was conducted on 30 patients with perforated acute appendicitis. 15 patients were in the control group and others 15 in the test group. In addition to standart treatment, surgery and antibiotics, the test group received pentoxifylline 0,5 mg/kgbw/day as an adjuvant for 2 days after the surgery. The end points of the study were to evaluate the condition of the wound in the 5th day after surgery. Evaluation include any infection or not in surgical site, and the severity of surgical site infection base on southampton classification. Both group were comparable in relation to surgical site infection. There were 10 male and 5 female patients in control group, and 12 male and 3 female in test group (p value 0,06). Mean age was 7 with SD 3,57 years in the control group and 7,6 with SD 3,24 in the test group (p value 0,596). In the control group 9 (60%) patients had wound infection and in the test group 5 (33,4%) patients had wound infection (p value 0,136). In control group 8 patients had 4th grade surgical site infection base on southampthon classification and 1 patient had 5th grade. In test group 4 patients had 3rd grade and 1 patient had 4th grade (p value 0,045). Pentoxifylline was not significantly to prevent surgical site infection (p value >0,05) but significantly decrease severity of surgical site infection (p value <0,05). Pentoxifylline improve the outcome by significantly decreasing severity of surgical site infection.*

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## I. Introduction

Acute appendicitis is the most common case of abdominal distress that requires immediate surgery because if it is not handled properly it will continue to be acute perforated appendicitis and intra-abdominal sepsis. The diagnosis of acute appendicitis in children is often difficult because classic symptoms such as lower right abdominal pain, vomiting and fever are often not found[1]. In addition to having difficulty getting the right history, in children acute appendicitis is rapidly perforated because the development of the omentum is not optimal. Acute perforated appendicitis has significant morbidity and mortality in the pediatric population[2]. In RSSA Malang during January 2008 to December 2015 there were 408 cases of pediatric appendicitis with 215 cases (52.6%) having perforated and sepsis. From the cases of appendicitis perforation in the last year there were 32% cases of surgical wound infection, higher than the existing literature, namely 5-20% [3]. Gram-negative bacterial infections such as those that occur in acute perforated appendicitis give rise to an inflammatory response that has special characteristics, including changes in leukocyte numbers, fever, hemodynamic disorders and disruption of the coagulation system, if it continues it will end in multi-organ failure. In general, gram negative endotoxin or lipopolysaccharide (LPS) is an agent that is considered responsible for the inflammatory response[4]. The inflammatory response that occurs after being triggered by the presence of inflammatory mediators results in activation of the coagulation cascade. The result of this coagulation cascade is thrombin. This thrombin will trigger changes in fibrinogen to fibrin. This fibrin will be deposited in the microcirculation[5]. Microcirculation guarantees tissue perfusion, fluid balance, distribution of oxygen and nutrients at the cellular level. Microcirculation plays an important role in wound healing and reduces the incidence of surgical wound infections[6]. Good perioperative management that can optimize microcirculation includes the use of balanced intravenous fluids, maintaining normal body temperature, pain management, and increased oxygen pressure at the tissue level[7]. In addition to microcirculation, fibrin deposits play an important role in the management of

intraperitoneal infections (peritonitis). Large numbers of bacteria hide in the fibrin matrix. These bacteria avoid the body's defense mechanism causes further infection[8]. Further intraperitoneal infection can be a risk factor for surgical wound infection. Experimental and clinical trials of pentoxifylline show effectiveness which means that in cases of gram negative infection as in the case of peritonitis due to perforation. The mechanism of action of pentoxifylline through increased fibrinolyticactivity, reduces fibrin deposits in the microcirculation while preventing the formation of fibrin and clots. In the end it will increase bacterial clearance, prevent further infection, and reduce the incidence of surgical wound infections[9].

## II. Material And Methods

This study was experimental and prospective studies to determine the relationship between the use of pentoxifylline and surgical wound infection in patients with acute perforated appendicitis.The number of samples was all patients who were included in the inclusion criteria during January 2017 to February 2018. The minimum number of samples according to the Roscoe formula was between 10-20, in this study using 30 samples in total, 15 samples without treatment and 15 samples treated with pentoxifylline. Subject of this studies was 3-18 years old patients who came to RSSA diagnosed with acute perforated appendicitis and performed appendectomy per laparotomy at IRD RSSA Malang.

**Study Duration:**January 2017 to February 2018.
**Sample size:** 30 patients.

**Inclusion criteria:**
1. Children 3-18 years old
2. Suspected acute perforated appendicitis
3. Surgery performed at IRD RSSA Malang with the findings of surgery was perforation in the appendix
4. Signed informed consent

**Exclusion criteria:**
1. Children 3-18 years old with a periappendicular mass, either periappendicular infiltrates or periappendicular abscesses
2. Other abnormalities found besides appendic perforation during surgery
3. Poor nutritional status
4. Having a chronic or moderate disease in the treatment of other diseases
5. Hemostasis disorders or require postoperative ICU care
6. Obtained the side effects of pentoxifylline drugs

**Procedure methodology**

After written informed consent was obtained, the samples was divided into 2 groups. The first group was the group with standard antibiotics until the fifth day added with the administration of pentoxifylline 1 mg / kg body weight / day to the second day. The second group was the group who were only given standard antibiotics until the 5th day.Then the surgical wound infection was evaluated until day 5.

**Statistical analysis**

Data was analyzed using SPSS. The difference in the incidence of surgical wound infection in acute perforated appendicitis of children receiving pentoxifylline therapy with those not receiving pentoxifylline therapy was analyzed by chi square testand the difference in severity of surgical wound infections in acute perforated appendicitis of children receiving pentoxifylline therapy with those not receiving pentoxifylline therapy was analyzed by Mann Whitney test. The level $P < 0.05$ was considered as the cutoff value or significance.

## III. Result

**Characteristics of the research sample**

This study was designed to determine the differences in the incidence of surgical wound infections after laparotomy appendectomy between patients with and without pentoxifylline adjuvant. This study was conducted in January 2017 to February 2018 on pediatric surgery patients in RSSA, obtained 38 patients with suspicion of perforated appendicitis. Some of our patients were excluded because they did not meet the criteria for being sampled in this study, including 3 patients because the findings during surgery were not perforated, 2 patients were perforated elsewhere, 2 patients had organ dysfunction, and 1 patient had poor nutrition. In the end 30 patients who met the inclusion criteria were sampled in this study.

Furthermore, 30 of these patients received education and were willing to take part in this study according to what was stated in the ethical feasibility attachment issued by RSSA. Samples were divided into 2 groups, 15 patients were included in the treated group and 15 patients were included in the treated group. From the sample of 30 patients the characteristics obtained as in Table 5.1 below.

**Table 5.1** Characteristics of the research sample

| | Untreated group | Treated Group | P value |
|---|---|---|---|
| Sex (%) | | | |
| - Men | 10(66,7) | 12(80) | 0,06* |
| - Women | 5(33,3) | 3(20) | |
| Average age ± SD (tahun) | 7 ± 3,57 | 7,6 ± 3,24 | 0,596** |
| Average duration of onset before surgery ± SD (hari) | 2,73 ± 0,59 | 2,86 ± 0,63 | 0,3** |

**Chi-square test*
*** t-test*

The average age in the untreated group was 7 years with a standard deviation of 3.57 years, whereas in the treated group it was 7.6 years with a standard deviation of 3.24 years (p = 0.596). Ratio in men compared to women in the untreated group 10: 5, while in the group with treated 12: 3.

**Surgical Wound Infection**

Of the 30 patients who participated in this study, 15 of our patients gave treatment in the form of intravenous pentoxyfillin adjuvant administration until the second day after surgery, wound evaluation was carried out during the 2nd and 5th day wound care. Day 5 wound care if there are no signs of infection is categorized as a group without surgical wound infection, but if signs of infection are obtained then an evaluation of the severity of the surgical wound infection is evaluated.

According to the Southampton scoring system, surgical wound infections are divided into 5 grade ie grade 1 if only erythema is found, grade 2 if erythema and other signs of inflammation are obtained, grade 3 if serous fluid is present, grade 4 if pus is obtained, and grade 5 if infection is heavy even to dehiscence or burst. From this study we obtained data related to surgical wound infections as listed in Table 5.2 and Table 5.3 below

**Table 5.2** Characteristics of patients who experience surgical wound infections

| | Surgical wound infection | | P value |
|---|---|---|---|
| | Untreated Group | Treated Group | |
| Sex | | | |
| - Men | 6 | 4 | 0,06 |
| - Women | 3 | 1 | |
| Age | | | |
| - 3-5 y.o | 3 | 2 | 0,59 |
| - 5-12 y.o | 5 | 3 | |
| - > 12 y.o | 1 | 0 | |
| Nutritional status | | | |
| - Malnutrition | 4 | 7 | 0,162 |
| - Normal nutrition | 1 | 2 | |
| - More nutrition | 0 | 0 | |
| Leukocyte | | | |
| - < 17.000 | 3 | 1 | 0,126 |
| - > 17.000 | 6 | 4 | |
| ASA status | | | |
| - 3 | 3 | 1 | 0,136 |
| - 4 | 6 | 4 | |
| Duration of surgery | | | |
| - 2,5 hours | 0 | 0 | 0,162 |
| - 3 hours | 3 | 1 | |
| - 3,5 hours | 3 | 3 | |
| - 4 hours | 3 | 1 | |
| Pus culture | | | |
| - E coli | 6 | 3 | 0,09 |
| - ESBL | 1 | 1 | 0,118 |
| - Pseudomonas Aeruginosa | 1 | 1 | 0,118 |
| - others | 1 | 0 | |
| Prehospital antibiotics | 5 | 2 | 0,07 |
| Sensitive with ceftriaxone | 5 | 0 | 0,028 |

**Table 5.3** Occurrence of surgical wound infection

| | Untreated group | Treated group | P value |
|---|---|---|---|
| Status of surgical wounds (%) | | | |
| - no surgical wound infection | 6 (40) | 10 (66,6) | *0,136 |
| - surgical wound infection grade 1 | 0 | 0 | |
| - surgical wound infection grade 2 | 0 | 0 | |
| - surgical wound infection grade 3 | 0 | 4 (26,7) | |
| - surgical wound infection grade 4 | 8 (53,3) | 1 (6,7) | |
| - surgical wound infection grade 5 | 1 (6,7) | 0 | **0,045 |
| Length of hospitalization ± SD (days) | 9,4 ± 4,64 | 6,4 ±1,88 | **0,137 |

**chi square test*
***mann whitney test*

The results of the statistical test analysis showed that there was no correlation between the administration of pentoxifylline and the incidence of surgical wound infection using the chi square test (p = 0.136).

The relationship between the administration of pentoxifylline and the severity of surgical wound infections that occurred using Mann Whitney test, obtained a p value of 0.045 indicating a difference in the severity of surgical wound infections between treated and untreated groups. The group who received pentoxifylline had a lower severity of surgical wound infection.

**Table 5.4** Differences in the severity of surgical wound infections

| | Average | Median | p value |
|---|---|---|---|
| Untreated group | 4,1 | Grade 4 | *0,136 |
| Treated group | 3,2 | Grade 0 (without surgery wound infection) | |

**mann whitney test*

The average length of hospitalization in the untreated group was 9.4 ± 4.64 days while in the treated group it was 6.4 ± 1.88 days. This studies shows that the treated group had shorter hospitalization rates compared to the untreated group, but this difference was not statistically significantly different from p value 0.137 (significant if p <0.05).

**Table 5.5** Difference in length of hospitalization

| | Average | Median | p value |
|---|---|---|---|
| Untreated group | 9,4 days | 9 days | *0,137 |
| Treated group | 6,4 days | 6 days | |

**chi square test*

## IV. Discussion

The prevalence of surgical wound infections after surgery for appendicitis laparotomy in RSSA ranges from 32-42% per year. This is higher than in the United States, which is 2-4% [10], and higher than Vietnam, which is 10.9% [11].Prevention of surgical wound infection using prevention NICE (National Institute for Health and Care Excellence) guidelines consists of three phases, namely the preoperative, intraoperative and postoperative phases. Preoperative phase includes taking a shower before surgery, shaving hair around the operating site on the day of surgery, special clothing for patients and operating room staff, removing jewelry, and using prophylactic antibiotics. The intraoperative phase includes hand washing, disinfection and demarcation of the operating field, sterile gowns and gloves, good hemostasis, irrigation, and wound dressing. Postoperative phase includes wound care, and empirical antibiotics in the event of a postoperative infection.

Giving medical treatment as part of prevention of surgical wound infections is still limited to prophylactic antibiotics. There is no medical method that is used to prevent surgical wound infections. Pentoxifylline is an agent that is being investigated about its role in preventing surgical wound infections, but this study has not been able to show that these agents can prevent surgical wound infections.Pentoxifylline is a drug commonly used in problems related to vascular system abnormalities, including peripheral vascular disease, cerebral blood flow, but experimentally and clinical trials show its effectiveness in the management of infectious cases such as perforation peritonitis, gram negative sepsis and other serious conditions.

In this study, we used pentoxifylline as an adjuvant to standard therapy of pediatric patients with perforated appendicitis. Recommendation doses for intravenous administration range from 0.5 to 1 mg / kg / day, we take the lowest dose regimen of 0.5 mg / kg / day by continuous drip 48 hours postoperatively, because at that time the phase of hemostasis wound healing occurs. Pentoxifllyne side effects include tachycardia, flushing, hypotension, and vomiting. But in this study, none of the patients who received pentoxifylline

experienced these side effects.Pentoxifylline catch points through several mechanisms including increasing fibrinolytic action, microcirculation repair, increased bacterial clearance, changes in physiology of fibroblasts in wound healing. In this study we focused on the fibrinolytic properties of pentoxifylline, and their relevance to the incidence of surgical wound infections and the severity of surgical wounds infection.

The mechanism of action of pentoxifylline is related to prevention of surgical wound infections through several paths including; 1. Increasing fibrinolytic activity in the peritoneum which is inflamed, this reduces the level of fibrinogen. This fibrinogen during inflammation will turn into fibrin, so that with reduced fibrin it can prevent entrapment bacteria.2. Prevent thrombosis in subperitoneallymphatics so that it improves microcirculation. Ultimately it will increase the bactericidal effect of therapeutic agents.Svanes et al. documented the possibility of complications in cases of peritonitis undergoing surgery more than 12 hours after onset[9]. The number of complications increases 3-fold and the length of hospitalization increases 2-fold. In this study, data were obtained that patients who underwent surgery in 2 days from onset did not have complications of surgical wound infection. In the untreated group, the mean was 2.73 days with a standard deviation of 0.59 days and 1 patient (6.67%) experienced a delay. In the treated group, it was obtained a mean of 2.86 days with a standard deviation of 0.63 and 2 patients (13.33%) experiencing delays. Patients who experience delayed surgery, all experience surgical wound infections later on.

In this study of a total of 30 patients, 14 patients had surgical wound infections, 5 of which occurred in the treated group. Shukla et al stated that the use of pentoxifylline can reduce the incidence of surgical wound infections[12]. In the study it was found that the incidence of surgical wound infection was lower in the treated group (5/14, compared to 9/14). This relationship was found to be p value> 0.05, meaning that the relationship did not reach statistical significance. The administration of pentoxifylline as an adjuvant does not affect the incidence of surgical wound infections in acute appendicitis perforated children. This is because the causes of surgical wound infections are influenced by many factors that are interrelated with each other.

Although the exact cause of infection of the surgical wound is difficult to determine, the cause is often associated with microbial flora and patients, surgical staff, surgical techniques, environment and patient factors as host[13]. Two factors that play an important role in influencing the incidence of surgical wound infections are endogenous and exogenous factors. Endogenous factors are factors that exist in patients such as immune status and nutritional status while exogenous factors are factors outside the patient such as length of hospitalization, level of cleanliness of the wound, compliance with aseptic techniques, duration of surgery, and postoperative wound care.Surgical wound infection is an unexpected event that occurs in hospitalized patients after surgery, and is one of the most common surgical complications [14]. Risk factors for surgical wound infection in surgical patients are generally divided into 3 parts, namely preoperative, intraoperative, and postoperative. Preoperative surgical wound infection factors include type of surgery, nutritional status, wound classification, ASA status, comorbid diabetes, cancer and leukocyte numbers. Intraoperative surgical wound infection factors include blood loss volume, length of operation, type of anesthesia, sterilization of instruments, operating rooms and surgical techniques. Postoperative factors of surgical wound infection include blood transfusion, and wound care[15].

The presence of confounding factors in this study has been minimized by not including in the study of patients with poor nutritional status, having chronic or moderate disease in treatment that can affect wound healing, other abnormalities found during surgical and patients with ASA 5 status.In this study, for preoperative surgical wound related factors, there were several things that became confounding variables in this study, including nutritional status. Nutritional status is assessed based on anthropometric BB / TB according to WHO provisions. According to the anthropometric guidebook on child nutrition assessment issued by the Ministry of HealthRepublic of Indonesia, nutritional status is divided into 5 categories, namely malnutrition, lack, normality, overweight and obesity. In this study, poor nutritional status is included in the exclusion criteria, because malnutrition can be a confounding factor in this study.

Nutritional status affects wound healing and is a risk factor for surgical wound infections [15]. In this study for underweight, normal and more nutritional status there was a non-significant relationship ($p = 0.162$). Similar to the study by Porras et al., It was reported that there was no correlation between nutritional status based on anthropometry and the incidence of surgical wound infection[16]. In line with the research of LinaHaryanti et al in the surgical section at RSCM, it was reported that there was no relationship between under nutrition and good nutrition with the incidence of postoperative abdominal wound infections[17]

The leukocyte number is a risk factor for future surgical wound infections[15]. Below is a table related to leukocyte values and the occurrence of surgical wound infections The leukocyte value is a stable, well-standardized, widely available, easy and inexpensive application, a biomarker of inflammation[18]. In this study the relationship between leukocyte values and surgical wound infection was not significant ($p = 0.162$). In this study, the mean leukocyte value in patients with surgical wound infections was 19477.86 uL with a standard deviation of 6071.42 uL, whereas in patients without surgical wound infection the leukocyte average was 16,370 uL with a standard deviation of 5777.35 uL.

Based on previous research by Heru in RSSA, the cut-off point for acute appendicitis and acute perforated appendicitis was 17,000. In this study all patients experienced leukocytosis, with the cut off point found in patients with leukocytes> 17,000 obtained 71% sensitivity and specificity 43.75% in predicting the incidence of surgical wound infection. Besides that, the positive predictive value 52.63% and NPV (negative predictive value) 63.63% were obtained.The American Society of Anesthesiologist (ASA) score evaluates the patient's status regarding comorbidities, making it a good predictor of the occurrence of surgical wound infections. The incidence of surgical wound infection is significantly higher in ASA 2-5 than in ASA 1, indicating that the ASA score before surgery has an influence on surgical wound infection[19]. In this study ASA scores ranged from ASA 3 and ASA 4. ASA 5 in patients with acute perforated appendicitis was the exclusion criterion in this study. Below is a diagram related to ASA scores and the occurrence of surgical wound infections. In this study the relationship of the ASA score with the incidence of surgical wound infection was statistically not significant with p = 0.136.

The subjects in this study who had surgical wound infections had ASA 3 and 4 scores. There was no association in this study, even though the United States National Nosocomial Infection Surveillance (NNIS) included ASA scores as one of the risk factors for surgical wound infections[20]. Similar to research by Duque in Brazil and Porras in Mexico.In this study for intraoperative surgical wound related factors there are several things that become confounding variables in this study, including the length of operation (operative compatibility). The duration of surgery more than 2 hours previously has been reported to be related to surgical wound infection, this is caused by the increased length of time exposed by microorganisms in the operating room[21].In patients with surgical wound infections the average duration of operation was 3.5 hours with a standard deviation of 0.39 hours and a median value of 3.5 hours. In patients without surgical wound infections, the average length of operation was 2.9 hours with a standard deviation of 0.2 hours and a median value of 3 hours. The relationship of duration of surgery with the incidence of surgical wound infection was not significant with p = 0.162.

Surgical wound infection in postoperative patients laparotomy appendectomy is inseparable from the microbes of the enterobacteriaceae (Coliform) gastrointestinal tract and anaerobic bacteria[22]. In the culture specimens on the pus obtained by surgery durante is a microorganism that causes infection of the surgical wound, considering that the culture in the wound wound of the surgical wound is a microbe from the gastrointestinal tract. In this study the results of cultures that were sensitive to ceftriaxone obtained surgical wound infections later in 5 patients, and all were obtained in the untreated group. This supports that pentoxifylline functions as an adjunct in improving the performance of the antibiotics used. In the end, surgical wound infection does not occur.

Krobot et al conducted a multicentre study of 162 patients with acute perforated appendicitis, reported that parenteral antibiotic therapeutic conformity was a predictor in preventing surgical wound infections and shortening hospitalization[23]. In this study patients who were given antibiotics according to culture were found in 15 patients. Of the 15 patients there were 5 patients experiencing surgical wound infections even though empiric antibiotics were given according to the culture results and the 5 patients were not treated with pentoxifylline. The relationship between surgical wound infection and sensitivity to empirical antibiotics was statistically significant with p = 0.028.In the untreated group 9 surgical patients were infected, consisting of 8 4th and 1st degree patients. However, in the treated group there were 5 patients with surgical wound infections, consisting of 4 third and 1 degree patients. The relationship between pentoxifylline and the degree of infection of the surgical wound obtained p value <0.05, meaning that the relationship was statistically significant.

The median degree of surgical wound infection in the untreated group was at level 4, whereas in the treated group it was at degree 0 or without surgical wound infection. In this study pentoxifylline cannot prevent the occurrence of surgical wound infections, but can reduce the degree of surgical wound infection that occurs. This is due to the role of pentoxifylline in fibrinolytics, so that infectious bacteria cannot hide in fibrin formed during the healing process. In addition, pentoxifylline improves microcirculation which causes antibiotics to be well distributed and increases the bactericidal effect.Surgical wound infections lead to longer hospitalizations, and maintenance costs increase. In this study, 16 patients were not found in the surgery wound infection(6 patients in the untreated group and 10 patients in the treated group) and 14 patients were found in the surgery wound infection(9 patients in the untreated group and 5 patients in the treated group). The average duration of hospitalization in patients who did not have surgical wound infections was 5.18 days, whereas in patients with wound infections the operation was 11 days.Higher degrees of severity will increase the morbidity and mortality associated with these patients. In this study there were 3 degree surgical wound infections in 4 patients, with an average of hospital stay was 8 days. 4th degree surgical wound infection in 9 patients, with an average hospitalization period of 11.8 days. Grade 5 surgical wound infections were obtained in 1 patient which caused the patient to die during treatment on day 16.

Withpentoxyfilline, the antibiotics can work better. The mechanism of action of pentoxifylline is by preventing the occurrence of thrombosis in the lymphatic subperitoneal so it will improve microcirculation.

Ultimately it will increase the bactericidal effect of therapeutic agents. In this study if the results of the culture are in accordance with the empirical antibiotics given, then this pentoxifylline can improve the bactericidal effect of antibiotics and prevent surgical wound infections.Pentoxyfilline in terms of price can be affordable by the lower middle class. The price of 1 ampoule pentoxifylline is around 40 thousand rupiahs, on average it takes 2-4 ampoules in the treatment period. Based on this study, the use of pentoxifylline can reduce the severity if an surgical wound infection occurs and shorten the duration of hospitalization.

## V. Conclusion

The administration of pentoxifylline cannot reduce the incidence of surgical wound infections children but can reduce the severity of surgical wound infections in acute appendicitis perforate children

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