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Research Article

Analysing the Effect of Prophylaxis Antibiotic Administration on Pediatric Clean Surgery Based on Post Operative Response of Neutrophil, Monocyte, and Lymphocyte, and Surgical Site Infection Rate

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Abstract: Insignificant administration of antibiotic leads to higher health cost and increase of antibiotic resistance. National prophylaxis antibiotic guideline on clean surgery amongst developed countries are varies meanwhile most developing countries still do not have any and adopt the established guidelines, not to mention there is not many specific guidelines for pediatric procedure. In Indonesia, 30% to 80% antibiotic usage was proven unnecessary.

This study analysed the effect prophylaxis antibiotic administration on pediatric clean surgery based on post operative response of neutrophil, monocyte, and lymphocyte, as the parameters of cell-mediated inflammatory response on tissue injury or infection, and surgical site infection rate.

A double blind randomized clinical trial was conducted from May 2013 to April 2014 at multi-hospital in Medan, Indonesia. Total sample is 42 subjects, distributed evenly into 2 groups. Post operative blood sample was examined on 3rd day and surgical wound was evaluated until 30th day.

Both groups were comparable in patients' demographic, clinical characteristic, and surgery procedure. Post operative rates of neutrophil, monocyte, and lymphocyte are not statistically different between groups (*P* = 0.083, *P* = 0.121, dan *P* = 0.486). Pre and post operative difference rates of neutrophil, monocyte, and lymphocyte are not statistically different between groups (*P* = 0.065, *P* = 0.294, dan *P* = 0.367). Surgical wound complication was 2.4% of total 42 sample (P = 1,00) with 0% surgical site infection event on both groups. This study recommends prophylaxis antibiotic administration on pediatric clean surgery is not necessary.

Keywords : prophylaxis antibiotic, pediatric clean surgery, cell-mediated inflammatory response, surgical site infection.

I. Background

Insignificant administration of antibiotic leads to higher health cost and increase of antibiotic resistance. On clean uncomplicated surgery, neither prophylactic or post operative administration of antibiotic is recommended in most developed countries national guidelines. However, clinicians, especially in developing countries do not give up this traditional practice easily despite the fact that recent meta-analysis and reviews support this view.[1] In Indonesia, a study conducted in two university hospital proved 30% to 80% antibiotic use was not as indicated.[2] Unindicated antibiotic use increases prevalence of microbial resistance to the antibiotic agent, and even can contributes as predisposition factor of patient infection, e.g. antibiotic-associated colitis caused by *Clostridium difficile*.[3][4]

Clean surgical wound (grade I) is wound created at an area where inflammation process is not present, does not enter into gastrointestinal or urogenital tract, and no failure of aseptic techniques in the operating room.[5] On clean surgery (grade I), antibiotic practice either as prophylaxis or adjuvant is no longer recommended.[6] A critical appraisal study in Switzerland even recommended reconsideration of prophylaxis antibiotic administration in pediatric appendectomy surgery, despite its classification as clean-contaminated surgery (grade II) and stated that no evidence that recommendations for prophylaxis antibiotic for an adult population can be transferred to children and that general recommendations concerning antimicrobial prophylaxis must be considered carefully for this age group.[7] Despite various guidelines in many developed countries, prophylaxis antibiotic administration in clean surgery is no longer recommended (grade A recommendation).[3][8] Until now, post operative prophylaxis antibiotic does not prove providing additional benefit, and this practice should be reduced, as it is costly and associated with an increase of antimicrobial resistance.[9]

By definition, the use of prophylaxis antibiotic is the use of antibiotic before, during, or after a diagnostic, therapeutic, or

surgical procedure, to prevent infectious complications. Prophylaxis can be divided into primary prophylaxis, secondary prophylaxis, and eradication.[8] The use of prophylaxis antibiotic to reduce surgical site infection rate on clean surgery remains a controversy because there are still many differences in operational restrictions on the surgery. However, the administration of these antimicrobial agents should not be used in routine conditions (e.g., in pediatric and young adult patients).[9]

One of the body's response to tissue injury, either due to trauma or surgery, or to infection is by activation of the immune system through cell-mediated inflammatory response. The active cells in this body response include neutrophils, monocytes, and lymphocytes. Circulating neutrophils, monocytes, and lymphocytes are inflammatory cells that immediately invade wounds after tissue trauma.[10][11]

Based on reasons described above, we measured the effect of prophylaxis antibiotic against cell-mediated inflammatory response, by comparing pre and post operative difference of neutrophil, monocyte, and lymphocyte, and surgical site infection rate on pediatric clean surgery with and without the use of prophylaxis antibiotic.

II. Aim

To compare the effect of prophylaxis antibiotic against post operative response of neutrophil, monocyte, and lymphocyte, and surgical site infection rates on pediatric clean surgery with and without the use of prophylaxis antibiotic.

III. Methods

A double blind randomized clinical trial with independent numerical and categorical variable analysis was conducted from May 2013 to April 2014 at university network hospitals in North Sumatera, Indonesia. Total sample is 42 subjects who were willingly to participate until the end. Subjects were distributed evenly into 2 groups, group with prophylaxis antibiotic (Group 1) and without prophylaxis antibiotic (Group 2). Pre operative blood sample was obtained up to three days prior to surgery, subjects meeting the inclusion criteria were admitted to hospital one-day prior to surgery and discharged home one-day post operatively. All subjects received equal pre and post operative treatment except for prophylaxis antibiotic which was administered as per group. Antibiotic used as prophylaxis was intravenous cephazolin (1^{st} generation cephalosporin) as recommended by The Ministry of Health of Indonesia (Permenkes RI No. 2406 Tahun 2011). Post operative blood sample was examined three days after surgery during first time ambulatory check-up. Surgical wound was evaluated, screened for complication, and assessed using Southampton wound scoring system. Surgical wound evaluation for complication was assessed on subject complaint basis until post operative day 30.

Pre and post operative neutrophils, monocytes, and lymphocytes level was collected and assigned separately according to each respective subject groups. All data was processed, analysed, and presented by computerized statistical program using independent numerical and categorical comparative test.

IV. Results

The overall number of subjects was 42 pediatric patients with 36 boys and 6 girls. By age, the lowest age was 1 month and the highest age was 14 years. The mean age of the subjects was 46.46 (SD 42.17) months.

Total 42 subjects distributed evenly into group with antibiotic (Group 1) and without antibiotic (Group 2), both group were comparable in patients' demographic, clinical characteristic, and surgery procedure (Table I).

Table I Subject characteristic

Characteristic	with antibiotic (Group 1) *n* (%)	without antibiotic (Group 2) *n* (%)	*P*
Sex			1.00
Male	18 (85.7)	18 (85.7)	
Female	3 (14.3)	3 (14.3)	
Age (month)			0.539
1—12	6 (28.6)	3 (14.3)	
12—60	11 (52.4)	13 (61.9)	
> 60	9 (19.0)	5 (23.8)	
Diagnosis			
Lateral inguinal hernia	14 (66.7)	14 (66.7)	0.666
Hydrocele	2 (9.5)	1 (4.8)	
Hemangioma	2 (9.5)	2 (9.5)	
Undescended testicle	0	1 (4.8)	
Benign Soft Tissue Tumor	2 (9.5)	2 (9.5)	
Others	1 (4.8)	1 (4.8)	
Procedure			
Herniotomy	14 (66.7)	14 (66.7)	0.579
High ligation	2 (9.5)	1 (4.8)	
Excision	4 (19.0)	4 (19.0)	
Orchidopexy	0	1 (4.8)	
Others	1 (4.8)	1 (4.8)	

The most common diagnosis was the lateral inguinal hernia (14 subjects), equal in number in both groups. Patients with diagnosis of lateral inguinal hernia underwent herniotomy (28 patients). Others consisted of herniotomy and orchidopexy procedures in a patient with lateral inguinal hernia and undescended testicle, and umbilical ligation in a patient with uncontrolled umbilical bleeding. The operative management data between the two groups had the same variance.

As shown on Table II to IV, the post operative rates of neutrophil, monocyte and lymphocyte were analysed and show no significant difference between study groups (P = 0.083, P = 0.121, dan P = 0.486).

Table II Post operative rates of neutrophil

	n	Mean (SD)	Mean difference (*CI* 95%)	*P*
Group 1	21	49.07 (SD 9,99)	6.08 (-12.99—0.83)	0.083
Group 2	21	55.15 (SD 12,07)		

Unpaired *t* test

Table III Post operative rates monocyte

	n	Median (min—max)	Mean (SD)	*P*
Group 1	21	5.30 (4.0—11.0)	5.52 (SD 1.50)	0.121
Group 2	21	4.50 (2.6—18.3)	5.62 (SD 3.30)	

Mann-Whitney U test

Table IV Post operative rate of lymphocyte

	n	Mean (SD)	Mean difference (*CI* 95%)	*P*
Group 1	21	43.62 (SD 10,14)	2.86 (-5.37—11.09)	0.486
Group 2	21	40.76 (SD 15,67)		

Unpaired *t* test

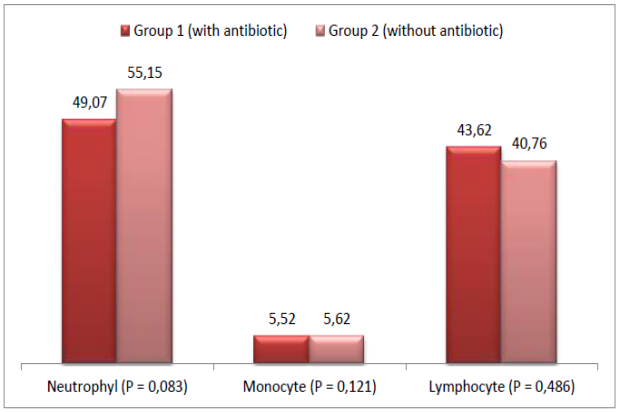

Figure 1 Post operative rates of neutrophyl, monocyte, and lymphocyte between two groups

Table V to VII presents the analysis results of pre and post operative difference rate of neutrophil, monocyte, and lymphocyte between groups. The results show no significant difference between study groups ($P = 0.065$, $P = 0.294$, dan $P = 0.367$).

Table V Pre and post operative rate difference of neutrophil

	n	Mean (SD)	Mean difference (*CI* 95%)	*P*
Group 1	21	4.83 (SD 1.08)	4.26 (-2.86—0.01)	0.065
Group 2	21	9.09 (SD 2.76)		

Unpaired *t* test

Table VI Pre and post operative rate difference of monocyte

	n	Median (min—max)	Mean (SD)	*P*
Group 1	21	0.50 (0.0—37.4)	2.28 (SD 8.06)	0.294
Group 2	21	0.80 (0.0—5.3)	1.05 (SD 1.16)	

Mann-Whitney U test

Table VII Pre and post operative rate difference of lymphocyte

	n	Mean (SD)	Mean difference (*CI* 95%)	*P*
Group 1	21	4.59 (SD 1.34)	2.77 (-1.87—0.05)	0.367
Group 2	21	7.36 (SD 1.98)		

Unpaired *t* test

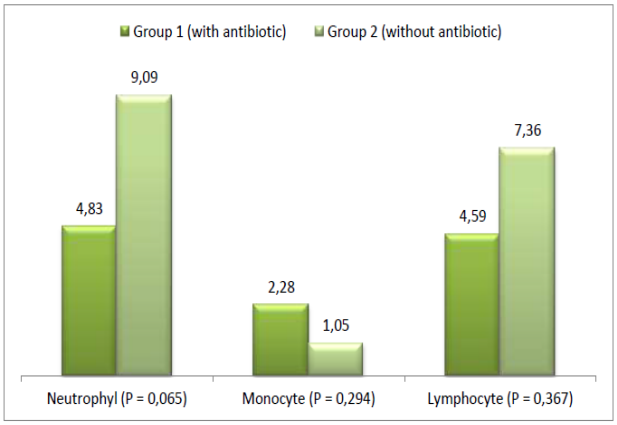

Figure 2 Pre and post operative rate difference of neutrophyl, monocyte, and lymphocyte between two groups

Surgical wound variables were analysed as depending variables of prophylaxis antibiotic use. Data analysis on the association of surgical wound conditions to antibiotic prophylaxis use are presented in the following table.

Table VIII Association between prophylaxis antibiotic administration with surgical site infection rate

		Surgical wound				*P*
		No complication		Minor complication		
		N	%	*n*	%	
Group	With antibiotic	21	100	0	0	1.00
	Without antibiotic	20	95.2	1	4.8	
Total		41	97.6	1	2.4	

Fisher's Exact test

Table VIII presents the analysis results of antibiotic prophylaxis use against the incidence of surgical site infection

rate. Minor complication occurred on grade I wound surgery was bruise, based on the Southampton wound scoring system. The analysis results show no significant relationship between antibiotic prophylaxis use against the surgical site infection rate on pediatric clean surgery.

Demographic and surgery procedure were also analysed using bivariate analysis to determine the association with post operative changes rates of neutrophil, monocyte, and lymphocyte. The results of data analysis are presented in the following table.

Table IX Association between demographic data and surgical procedure with post operative changes in neutrophil, monocyte, and lymphocyte levels

	Changes of level (*P*)		
	Neutrophil	Monocyte	Lymphocyte
Sex[a]	0.854	0.928	0.393
Age (month)[b]	0.784	0.445	0.333
Surgical procedure	0.004	0.701	0.055

[a]Mann-Whitney U test
[b]Kruskal Wallis test

The results show no significant association between sex and age to post operative changes in neutrophil, monocyte, and lymphocyte levels. Surgical procedure revealed significant association with changes in neutrophil levels obtained in post operative day 3.

V. Discussion

Since the beginning of the last decade, a lot of health service centres in various parts of the world have studied about the correct use of antibiotic prophylaxis. Various guidelines have been published, not only regional but also national. Nevertheless, a lot of published guidelines still doesn't make surgeons follow the recommendation of guidelines.[9] Although many studies have shown low level of infection for surgical wound grade I (1 -5%) and the use of antibiotic prophylaxis is not proposed any more,[6] the anxiety of possible surgical wound infection was often filled in surgeons mind in spite of knowing about the possibility of contamination and surgical wound grading according to the surgery procedure. Surgeons especially in developing countries still cannot leave the tradition of antibiotic usage that tends to waste the "availability" of antibiotics.[1] Many regional and national published guidelines doesn't compose of a specific guideline that has been studied in the population of pediatric patients. There hasn't been much evidence of the effectiveness of the use of prophylaxis antibiotic pediatric patients so most of the guidelines still used the evidence of antibiotic prophylaxis effectiveness in adults.[3]

In a clean surgical procedure—which is designed to prevent infection—antibiotic use was unnecessary and has not been recommended by guidelines of antibiotic prophylaxis use [3][4] despite known anti-inflammatory effects on antibiotics in non-infectious conditions. The analysis of post operative rate of neutrophil, monocyte, and lymphocyte between subjects of Group 1 and Group 2 (Table II to IV) showed no significant mean difference. Based on this data, it can be hypothesised that in Group 1, antibiotic prophylaxis use did not result in lower post-operative cell-mediated inflammatory response levels than in Group 2. Cell-mediated inflammatory response worked without being affected by the use of antibiotic to counter inflammation and susceptibility of infection in clean surgical procedure. It was also shown that there was no significant difference in the surgical site infection rate between groups with antibiotic use and without antibiotic use (Table VIII).

The indicated results—no significant difference in post operative rate of neutrophil, monocyte and lymphocyte as the component of cell-mediated inflammatory response on pediatric clean surgery in groups with antibiotics and without antibiotics (Table II to IV)—showed that in clean surgery, the inflammatory response of body tissues is sufficient to counter the occurring inflammation due to post operative tissue injury without the need for antibiotic prophylaxis use. In this study, the incidence of surgical site infection was 0% in both test groups, compared with the rate of infection in clean surgery (grade I) of 1.0-5.4%[6] and 3.9% in the group with antibiotics and 5.8% in the non-antibiotic group in a similar study by Shah JN, et al (2012).[1] The results of this study are in line with the clean surgery guideline recommendation which states prophylaxis antibiotic is not required, [3][4] but in contrary to the recommendation guidelines issued by the United States,[8] which recommends administration of cefazolin prophylaxis in clean surgery on the inguinal region.

Table IX proved that post operative changes in neutrophil, monocyte, and lymphocyte levels were not associated with subjects' sex and age. Significant association of surgical procedure with post operative changes in neutrophil levels consistent with the immediate response of cell-mediated inflammatory components to the tissue injury. As this study post operative blood sample was obtained on the post operative day 3, neutrophil would already reached the peak level by the time.[10][11]

Another issue about antibiotic usage is physician compliance. As stated before, surgeons' anxiety about the susceptibility of infection towards their surgical wound overcome the fact about surgical site infection rate on the clean surgery procedure performed. Brusafero, et al documented increase insignificant proportion about the proper use antibiotic prophylaxis, from 31% to 45%. Kim reported low compliance of prophylaxis antibiotic use as recommended by the guideline in many surgical clinics (36%). The level of compliance was very low compared to the recommendation of therapeutic antibiotic use in non-surgical patient.[9] The reason of this low compliance can be researched further.

Based on this study data results, we recommend that

prophylaxis antibiotic administration on pediatric clean surgery is not necessary. This study data can be used as a one of basis data in creating guideline of practice of prophylaxis antibiotic in pediatric patient, especially on pediatric clean surgery (grade I surgical wound) in our university network hospitals, and also possible for other centres. Proper use of prophylaxis antibiotic can reduce the incidence of antibiotic-side effects, decrease the rate of bacterial resistance, and make a major contribution to the healthcare budget savings.

Some study limitation

This study has several limitations related to the sampling of subjects. This study initially designed to obtain sample only from our university main hospital which is the province referral hospital in order to minimalized the bias factor of blood sampling, operation room standard, and post operative treatment room. But as the uncomplicated pediatric clean surgery is mostly performed in the district hospital, the sample quota was hard to be fulfilled within the study given timeline. As a result, this study collected samples from university network district hospitals across the province. We are aware of this sampling method resulting in various location of laboratory blood sampling, and different operating room and treatment room conditions due to differences in hospital accreditation marks. This limitation resulted in a bias that although can be restricted by a randomized clinical trial, will not produce output as good as the results obtained by sampling from a single healthcare service. Other limitation in this study included funding aspect related to the cultural aspects of the subjects, resulting post operative blood sampling was performed only once, on the post operative day 3. Although laboratory examination and accommodation cost of subjects were sponsored by the researcher, the cultural aspect of the subjects, such as the far distance between living location to the healthcare location, thus requires more time and accommodation costs, also the reluctance of having repeated blood shot, resulting in subjects' objection to return to do repeated blood sampling for the second time. This resulted in a low accuracy of monocyte and lymphocyte levels because the sampling was performed before the level of these components reach their peak in circulation. For more accurate level of cell-mediated inflammatory response components, based on the literature used on this study, post operative blood sampling should be performed at least twice, on the post operative day 3 and 7. Neutrophil peak levels in the circulation will be achieved in the shortest time, followed by monocytes and lymphocytes.

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