WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 11, 55-62. Research Article ISSN 2277– 7105

OPTIMIZATION REGIMENT THERAPY OF PROBIOTIC AND ANTIBIOTIC COMBINATION FOR ACUTE DIARRHEA IN CHILDREN

Dewa Ayu Swastini[1*], Cokorda Istri Sri Arisanti[1], Ngakan Gede Wahyu Indrayana[1], Sudiasmara I Wayan[1], Anak Agung Wiradewi Lestari[2],

[1]Biomedic and Clinical Pharmacy, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Udayana University.

[2]Functional Medical Unit Clinical Pathology of Medical Faculty Udayana University/ Sanglah Central General Hospital.

Article Received on
26 Aug 2015,

Revised on 15 Sep 2015,
Accepted on 06 Oct 2015

***Correspondence for Author**
Dewa Ayu Swastini
Biomedic and Clinical Pharmacy, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Udayana University.

ABSTRACT

Currently a new paradigm is developed in additional therapy for acute diarrhea which can prevent pathogen bacterial colonization that causing diarrhea known as probiotic. The most common cause of acute diarrhea was bacterial infection, wherein antibiotic was used to treat the infection. Antibiotic and probiotic have contrast activities, so far there is no any standard rules regarding therapy regiment of using probiotic and antibiotic that given in one prescription. Random selection was performed to 63 pediatric patients on public hospitals, diagnosed with acute diarrhea, and getting antibiotic and pro-biotic in one prescription. Patients were divided in to three group of regiment therapy: group 1 (get probiotic 2 hours before antibiotic), group 2 (get probiotic with antibiotic at same time) and group 3 (get probiotic 2 hour after antibiotic). The effectiveness of therapy was measured from frequency and the duration diarrhea, along with volume and consistency of feces. Recurrence was observed for 3 months after the administration of probiotic and antibiotic. Data was analyzed statistically using Kruskal-Wallis test method and continued with Mann Whitney test at $p < 0.05$. Overall research subjects mostly boys, majority experienced by infants between 6-12 months and cephalosporin was the type of antibiotic that most often prescribe. The regiment therapy of probiotic that given 2 hours after antibiotic was proven to have significant ability ($p < 0.05$) in lowering frequency and duration of diarrhea, improving volume and consistency of feces

compared to the administration of prebiotic 2 hours before antibiotic and in coadministration with antibiotic. There was not any different impact of regiment therapy from probiotic and antibiotic in one prescription to the recurrence of acute diarrhea on children.

KEYWORDS: probiotic, antibiotic, effectiveness, recurrence. acute diarrhea, children.

INTRODUCTION

Diarrhea still one of major problems on public health. The number of diarrhea occurrence in Indonesia from year to year tends to increase. According to morbidity survey conducted by Diarrhea sub-directorate, Health Department from 2000 until 2010 the trend of diarrhea occurrence was increased. In the 2000, the Incident Rate (IR) of diarrhea was 301/1000 of population and in 2010 becoming 411/1000 population. Futhermore, from the result of government research in 2007 showed that the highest cause of morbidity on infants (25.2 %) was diarrhea.

The major etiology of acute diarrhea which is often found in the field or clinically is caused by infection and poisoning (Indonesian Health Department, 2009). Antibiotic that prescribe to threat the infection usually doesn't have a specific target to eleminated the pathogen bacteria, so its can also cause the death of intestine's microflora that useful to keep body's homeostasis. Wanke, C.A. (1991) suggested some of the antibiotic associated on inducing diarrhea. Diarrhea occurred in about 5 - 10 % of patients treated with ampicillin, 10 - 25 % treated with amoxicillin clavulanat,15 - 20 % treated with cefixime, and 2 - 5 % treated with cephalosphorine, fluoroquinolones, azitromycin, claritromycin, erythromycin, and tetracycline. Therefore the use of antibiotic during the episode of acute diarrhea can increase the extend and diarrhea recurrence.

Currently a new paradigm is developed in additional therapy toward diarrhea, by maintaining good bacterial microecosystem in intestine, so that it can prevent pathogen bacterial colonization causing the diarrhea known as probiotic (Sudarmo S.M., 2003). Probiotic is a compound resulted from a microorganism that able to spur the growth of other microorganism, its can balance the population of microorganism in intestinal mucosa (Alasiry E., 2007). It is contrary with antibiotic activity, that will cause the death of pathogen and non-pathogen bacteria. The death of non-pathogen bacteria will disrupt the condition of normal intestinal microflora which resulted in the risk of prolonged diarrhea (Wanke, C.A., 1991). However in clinical practice, the probiotic and antibiotic often combined in one prescription

to treat diarrhea. So far there is no standard rules regarding therapy regiment of probiotic and antibiotic that given in one prescription. Antibiotic has varied half time (t ½) that is between 2–4 hours with onset ± 2 hours (Ganiswarna, 1995). Meanwhile probiotic also needs time for growth phase starting after 2nd hour of administration (Shantharam, 1997 in Nurhajati et al., 2009). Therefore, this research it will be observed the optimization regiment therapy of probiotic and antibiotic that given in one prescription through the effectiveness on treat diarrhea in children.

MATERIAL AND METHOD

a. Population Study and Data Administration

63 patients were selected randomly who fulfill the inclusion criteria and did not fulfill exclusion criteria for the period of March 2015 until August 2015. Inclusion criteria was that patient with age between 0 -12 years old, diagnosed with acute diarrhea and given antibiotic and pro-biotic therapy in one prescription, and agreed to sign an informed consent. Exclusion criteria was patient who allergic with antibiotic and had congenital abnormality in alimentary tract based on anamnesis and physical checking. Also for patient who had severe companion diseases such as loss of consciousness, hemodynamic disturbance, cardiovascular disorder and severe respiratory disorder and suffering from malnutrition. Patient who was getting therapy with other medication in addition to main therapy which causing side effect of diarrhea (such laxative) was excluded.

Regiment therapy in administering probiotic with antibiotic in one prescription was divided into three group: 1st group (get probiotic 2 hours before antibiotic), 2nd group (get probiotic with antibiotic at same time) and 3rd group (get probiotic 2 hour after antibiotic).

b. Statistic Analysis

The effectiveness of therapy was measured from frequency and the duration diarrhea, along with volume and consistency of feces, and also diarrhea recurrence. Recurrence was observed for 3 months after the administration of probiotic and antibiotic. Frequency, duration, and the recurrence of diarrhea was analyzed using one way anova followed with LSD at confidence level of 95%. Volume and consistency of feces was observed using scoring based on The Bristol Stool Form Scale (for children), and was analyzed using Kruskal-Wallis test continued with Mann Whitney with confidence level of 95%.

RESULT

a. The Characteristic of Research Subjects

The characteristic of 63 research subjects was divided based on gender, age and antibiotic prescribed. The majority of patients were boys (54%) with age between 6-12 months (37%) and using the most prescribed antibiotic was cephalosporin (cefixime and cefadroxil) (40%) (Table 1). Yusuf (2011) found that gender does not influence the occurrence of diarrhea on children that caused by rotavirus, meanwhile at age 6-12 children experience the weaning process, ie the process of cessation of breastfeeding gradually. At this age children start to given soften foods, began to crawl so that direct contact can occur. Additionally vulnerable contaminated tableware, also can increased the risk of diarrhea (Midthun and Black, 2000). Bakteri that often found to be the caused of acute diarrhea in children are *Shigella sp., E. Coli, Sallmonela, C. jejuni* and *Y. enterolitica* (Umar, 2004), and cephalosporin antibiotic usually used in therapy against *E. Coli* and *Shigella sp.* because of its effectiveness reaches 98%.

Table.1. The Characteristic of Research Subjects

Characteristics	N	%
Gender		
Male	34	54%
Female	29	46%
Total	**63**	**100%**
Age		
0-6 month	16	25%
6-12 month	23	37%
12- 24 month	10	16%
2-4 year	7	11%
4-8 year	5	8%
8-12 year	2	3%
Total	**63**	**100%**
Antibiotics		
Cefadroxil	16	25%
Cefixime	25	40%
Amoxicillin	13	21%
Thiamphenicol	9	14%
Total	**63**	**100%**

b. The Effectiveness of Therapy

The result of research shows that the lowest frequency of diarrhea, and a significant increase of volume and consistency of feces is achieved in the 3rd group that get (probiotic 2 hour after antibiotic) compared to 1st group (get probiotic 2 hours before antibiotic), 2nd group (get

probiotic with antibiotic at same time) (Table 2a and 2b). There is no significant difference between 1st group (get probiotic 2 hours before antibiotic) compared to 2nd group (get probiotic with antibiotic at same time) toward to frequency of diarrhea and the ability in increase the volume and consistency of feces (Table 2.b). Meanwhile, after three months observation, none of the patient get diarrhea recurrence.

Table.2a. The Frequency, Volume and Consistency of Feces on Acute Diarrhea in Children

Group	Frequency of Diarrhea (Mean ± SD)	Volume and Consistency of Feces (Mean ± SD)	Anova*/Kruskal-Wallis ** test (p)
1st group	4,35±0,296	2,07±0,097	p<0.05
2nd group	4,26±0,298	2,15±0,166	
3rd group	3,97±0,213	2,35±0,108	

Table.2b. The Comparison of Frequency, Volume and Consistency of Feces on Acute Diarrhea in Children between Regiment Therapy

Group	Frequency of Diarrhea (p<0.05)*		Volume and Consistency of Feces** (p<0.05)	
	2nd group	3rd group	2nd group	3rd group
1st group	0.257	0.001	0.091	0.000
2nd group		0.002		0.000
*Based on LSD test ** Based on Mann Whitney test				

DISCUSSION

Antibiotic is working as bakteriostatic or bacterisid that be able to killing pathogen bacteria inside the body. Antibiotic has varied half time (t ½), between 2-4 hours with the onset achieve in ± 2 hours, so that it is given several times in a day, to achieve Minimum Effective Concentration (MEC) (Sumadio and Harahap, 1994).

Antibiotic that prescribe to threat the infection usually doesn't have a specific target to eleminated the pathogen bacteria, so its can also cause the death of intestine's microflora that useful to keep body's homeostasis. In this research the 3rd group (use of probiotic 2 hours after antibiotic) provides the decrease of diarrhea frequency greater compared to the 1st group (use of probiotic 2 hours before antibiotic) and the 2nd group (use of antibiotic and probiotic at same time). The administration of probiotic 2 hours after antibiotic will restore normal intestinal flora by regrowing non-pathogen bacteria inside the intestine which have died due to antibiotic administration 2 hours prior, so that keeping the body's homeostasis. Meanwhile probiotic needs time for growth phase that began after 2nd hour of administration and

reaching maximum growth in the 18th hour, and will reach stationary phase about 20th - 22nd hour after administration (Shantharam, 1997 in Nurhajati et al., 2009).

In the 1st (probiotic given 2 hours before antibiotic), probiotic given previously will work to grow non-pathogen bacteria which will inhibit the growth of pathogen bacteria and prevent pathogen bacterial colonization causing the diarrhea (Firmansyah A., 2001). However 2 hours later when the growth phase of probiotic begins, and the patient consumes antibiotic, the antibiotic will eliminated all the bacterian include the good one. The death of non-pathogen bacteria will disturb the condition of normal intestinal micro-flora resulted in the risk of prolonged diarrhea (Wanke, C.A., 1991). Meanwhile in the 2nd group (antibiotic and probiotic given at the same time), antibiotic and probiotic consumed at the same time by patient will work as antagonist or opposing each other. Antibiotic works by inhibiting or killing microbe or other bacteria including non-pathogen bacteria, meanwhile probiotic works by growing non-pathogen bacteria to keep normal intestinal flora (Sumadio and Harahap, 1994), both of antibiotic and probiotic have average onset of $\pm$ 2 hours to give effect. When pro-biotic grows non-pathogen bacteria which will keep normal intestinal micro-flora, at the same time antibiotic will also kill pathogen and non-pathogen bacteria. This antagonist effect will cause the condition of intestinal micro-flora not to become return to normal and body's homeostasis is disrupted.

We found that probiotic given 2 hours after antibiotic give a significant increase of volume and consistency of feces, consistent with the statistical results of the frequency of diarrhea. Probiotic improve the absorption of nutrients and water, thus improving stool consistency (Firmansyah A., 2001). In addition, the decrease of diarrhea frequency will also improve the content and consistency of stool (Ngastiyah, 2005).

Recurrence is a persistent infection because of imperfect healing process, new infection by other pathogen, or food intolerance due to intestinal function not yet returning to perfect condition (Walker-Smith J., 1989). In this research diarrhea recurrence was not occurred in all group, so that administration time do not affect the diarrhea recurrence in child patient with acute diarrhea. In this research probiotic is given as therapy for $\pm$ 5 days. Casani (2007) stated that probiotic administration for $\pm$ 5 days with the dose of 5 x 10^9 Colony Forming Units (CFU) can prevent diarrhea recurrence for 3-4 months.

CONCLUSION

Difference role of regiment therapy using antibiotic and probiotic combination in one prescription, impress the effectiveness therapy of acute diarrhea on children. Probiotic that given 2 hours after antibiotic is proven to have significant impact ($p < 0.05$) in lowering diarrhea frequency and repairing the volume and consistency of feces compared to probiotic that given 2 hours before antibiotic, and probiotic and antibiotic that given at same time, in acute diarrhea on children. There is not any different impact of regiment therapy using antibiotic and probiotic combination in one prescription to the recurrence of acute diarrhea on children in pediatric.

ACKNOWLEDGEMENT

Research Institutions and Community Service Udayana University The hospital had given permission for conducting this research.

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