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Original Article

The efficacy of trimethoprim-sulfamethoxazole treatment in children with acute bloody diarrhea

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Abstract

Background The etiologies of bloody diarrhea are shigella, amoeba, enterocolitis, trichuriasis, and other causes i.e, EIEC, *Campylobacter jejuni* or rotavirus. In developing countries, trimetroprim-sulfamethoxazole (TMP-SMP) is effective in 80% of children with bloody diarrhea.

Objective To determine the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) treatment in children with acute bloody diarrhea.

Methods A randomized double blind clinical trial was conducted in Adam Malik Hospital and Dr. Pirngadi Hospital Medan during September 2003-March 2004. Children aged 2-24 months old with diagnosis of acute bloody diarrhea were randomized into two groups to either receive TMP-SMX or placebo for 5 days. Microscopic fecal analysis was performed on the first, second, fifth and twelfth day, and the results were compared.

Results A total of 68 children consisted of 48 (71%) boys and 20 (29%) girls were enrolled. Each group had 34 participants. Analysis of the first day showed leukocyte and erythrocyte in the stool specimens, which were all absent on the twelfth day in both groups. There was no difference in stool analysis between TMP-SMX and placebo group in day two (P=0.758), day five (P=0.341) and day twelve. Diarrhea duration in TMP-SMX and placebo group was 7.18 days and 6.65 days, respectively. This different was statistically not significant (P=0.385).

Conclusion There is no difference in the efficacy of trimethoprim-sulfamethoxazole treatment compared to placebo in children with acute bloody diarrhea. **[Paediatr Indones 2007;47:17-20]**.

Keywords: *acute bloody diarrhea, trimethoprim-sulfamethoxazole, fecal analysis, bloody stool*

Diarrhea remains one of the most common cause of morbidity and mortality in children in developing countries with up to one billion patients and 3 to 5 million deaths annually.[1] In Indonesia, 60 million patients with diarrhea were estimated every year and 70-80% of those affected children were under five.[2] Fifty percents of those children died and 10% of those children had bloody diarrhea.[3-6] The high incidence is related to low sosio-economic level, crowded areas, and poor hygiene and sanitation.[7-9]

The etiologies of bloody diarrhea are shigella, amoeba,[9-11] enterocolitis due to cow's milk allergy, trichuriasis and other causes, i.e, EIEC, *Campylobacter jejuni*[11-13] or rotavirus (*Edmunson*).[14] The main cause is shigella (shigellosis) which is usually a self limiting disease.[7-9] Antimicrobial drugs are administered only in severe patients with symptoms such as malaise, high fever, abdominal cramp, tenesmus, profuse bloody diarrhea, vomiting, and seizure. In developing countries, trimethoprim-sulfamethoxazole (TMP-SMP) is effective in 80% of

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children with bloody diarrhea.[15] The diagnosis of bloody diarrhea is based on the presence of bloody or mucous stool, leukocyte and erythrocyte in stool specimens. WHO 1990 suggested to give TMP-SMX to all children with bloody diarrhea without determining the cause.[10-13] The dose of TMP is 5-10 mg/kg/day and SMX 25-50 mg/kg/day in two divided doses for 5 days.[10] It was noted that clinical improvement began after 2 days; the fever decreased, relief of abdominal pain and absent of leukocyte or erythrocyte from microscopic stool specimens.[12] A study in Bangkok in 1972 reported that in children aged 3 months-12 years, 2-day treatment with TMP-SMX gave good results in 97% patients. If there was no improvement, treatment must be changed to metronidazole for the suspicion of amoeba even without stool culture.[16] The aim of this study was to determine the efficacy of trimetho-prim-sulfamethoxazole (TMP-SMX) in children with acute bloody diarrhea.

Methods

This was a randomized double-blind clinical trial. Subjects were children who visited Outpatient and Inpatient Clinic of Adam Malik Hospital and Dr. Pirngadi Hospital during September 2003–March 2004. We calculated sample size with sample power of 80%, Za=1.960 and Zb=0.842, and divided the subjects into two groups of TMP-SMX or placebo. Inclusion criteria were children aged 2–24 months, with diagnosis of acute bloody diarrhea (diarrhea <13 days) by microscopic stool analysis (the presence of leukocyte or erythrocyte more than 4/HPF in the stool specimen), and the parents signed informed consent. Children with persistent diarrhea or chronic diarrhea (more than 14 days), or children with any parasite found in macroscopic or microscopic stool specimen, or children who had been treated within 5 days before admitted to our hospital, were excluded. Ethical approval was obtained from the Ethics Committee of Medical Faculty of North Sumatra University.

All children with acute diarrhea (defined as watery stools >3 times per day in less than 14 days) and aged 2–24 months who came to the hospitals during September 2003–March 2004 were recruited for microscopic stool analysis. Stool specimens were treated immediately with eosin 1-2%.[17] Two specimens were made for each patient, one was analyzed by the authors and the other was by an analyst. The patients were enrolled if there were positive leukocytes and erythrocytes in their stool. We did not perform culture or proctosigmoidoscopy. Stool analysis was performed in day one, two, five, and twelve. The study subjects were randomized into 2 groups, to either receive trimetoprim-sulfametoxazole (TMP 5–10 mg/kg/day and SMX 25–50 mg/kg/day) syrup divided into two doses for five days or placebo syrup. One assistant was assigned to perform the randomization. Every bottle was coded and after drawing the number, we gave the patient a bottle of syrup. The assistant will open the code at the end of study. All children had standard treatment for diarrhea.

The patients were asked to come for follow up on day 2, 5 and 12. If they had objection, the follow up was made by home visit according to schedule.

Table 1. Characteristics of study subjects in intervention and placebo groups

Characteristics	TMP-SMX		Placebo	
	n	%	n	%
Age (months)				
2–11	16	47	15	44
12–24	18	53	19	56
Sex				
Boys	24	71	24	71
Girls	10	29	10	29
Nutritional state				
Normal	4	12	15	44
Mild Malnutrition	10	29	7	21
Moderate Malnutrition	12	35	7	21
Severe Malnutrition	8	24	5	15
Dehydration state				
Without Dehydration	6	18	15	44
Mild Dehydration	28	82	17	50
Severe Dehydration	0	0	2	6
Parental education				
Father				
Higher education	9	27	9	27
High School	22	64	22	64
Elementary School	3	9	3	9
Mother				
Higher education	7	21	8	23
Senior High School	24	71	21	62
Elementary School	3	9	5	15
Parental Occupation				
Father				
Employee	16	37	18	53
Casual Worker	18	53	16	47
Mother				
Employee	10	29	13	38
Housewife	24	71	21	62

Table 2. Distribution of leukocyte and erythrocyte found in microscopic stool analysis

	TMP-SMX group					Placebo group				
	positive		negative			positive		negative		P
	n	%	n	%		n	%	n	%	
Day II	27	79	7	21		28	82	6	18	0.758
Day V	9	27	25	73		12	35	22	65	0.431
Day XII	0	0	34	100		0	0	34	100	

Recovery was considered if there was no leukocyte or erythrocyte in stool analysis performed at day two, five, and twelve. Data was analyzed using SPSS for Windows version 11.0. Efficacy of treatment was analyzed by chi square and independet t-test comparing diarrhea duration, statistically significat if $P<0.05$.

Results

There were 68 patients enrolled, boys were twice as many as girls. Details of the study subjects in both groups are depicted in **Table 1**.

Results of microscopic stool analysis in day one were 100% positive while the result of day twelve were all negative. There was no significant difference in microscopic stool analysis between TMP-SMX group and placebo in day two ($P=0.758$), day five ($P=0.341$), and day twelve (**Table 2**). The mean diarrhea duration in group TMP-SMX was 7.18 (SD 2.63) days while in group placebo was 6.65 (SD 2.35) days, which was not significantly different ($P=0.385$).

Discussion

In this study, the medication was continued for five days although WHO suggested to change medication after two days if there is no improvement. On the other hand, our study showed that TMP-SMX was as effective as placebo in bloody diarrhea. Soeparto *et al*[10] mentioned that bloody diarrhea was not always caused by bacteria. In infants, it might be related to cow's milk or soy allergy.

The cause of bloody diarrhea in this study was not determined. This is one of the limitations of this study because we could not control hygiene and feeding practices at home. Soenarto *et al*,[18] reported that shigella was found in 41% patients of under five children with bloody diarrhea. The Department of Health also suggests administering TMP-SMX 5-8 mg/kg/day in all bloody diarrhea patients without isolating the agent. If there was no clinical improvement for two days, we should think of other factors.[19] The incidence was higher in non breastfeeding infants. The study also reported that acute diarrhea could also be caused by shigella and rotavirus in the same time. This study could not explain the influence of demographic factors in bloody diarrhea duration.

Boediarso[21] found bloody diarrhea in 2.8% of all children with diarrhea in RSCM Jakarta, about 18.3% of those were caused by *Shigella sp*. In the above study, the patients received ampicillin and TMP-SMX. They reported high resistancy to ampicillin compared to TMP-SMX. Suharleni[22] still noted the same conclusion in her study.

Dwipoerwantoro *et al*[23] (2003) reported that shigella was isolated in 48% out of 50 studied patients and 70% were resistant to TMP-SMX. Clinically, 83% patients had no bloody stool and only 25% patients suffered from tenesmus. Guerrero *et al*[24] in Mexico reported that there were specific symptoms of shigellosis. Fifty percent of patients were under 6 months and showed asymptomatic shigellosis, the symptoms appeared more in older children.

Triatmojo *et al*[25] noted that demographic factors had a role in antimicrobial resistancy. A longitudinal study might explain the role of demographic factors in the duration of bloody diarrhea and determine the definitive agent. Due to economic issues, TMP-SMX is still recommended in certain areas.

We have shown tha TMP-SMX was as effective as placebo in children with bloody diarrhea. We conclude that TMP-SMX is not effective in the treatment of bloody diarrhea in children.

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