

## Folic acid and acute diarrhea in children

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### Abstract

**Background** Diarrhea has been a health problem in children under five year old. Although the mortality caused by acute diarrhea has fallen worldwide, the mortality has increased in developing countries, such as Indonesia.

**Objective** To assess the effect of folic acid in reducing the severity of acute diarrhea in children.

**Methods** This study was a single-blind, randomized control trial in children with diarrhea aged six months to five years at a local government clinic in the Secanggang District, Langkat Regency, North Sumatera Province from August 2009 until January 2010. Subjects were recruited by consecutive sampling then randomized into two groups. Of the 112 children who participated, 56 children received oral folic acid and 56 children received placebo, 1 capsule per day for five days. The statistical analyses used were the independent T-test and Chi square test with 95% confidence intervals (95% CI) and P values < 0.05 considered to be statistically significant.

**Results** There were significant differences between the folic acid and placebo groups with regards to stool consistency (P=0.02), diarrheal volume on the second day [147.52 vs. 303.21 mL, respectively, (P=0.001)], frequency of diarrhea on the third day [1.9 vs 2.8 episodes, respectively, (P= 0.001)], duration of initial treatment to recovery [91.3 vs. 117.9 hours, respectively, (P = 0.001) and the total duration between initial symptoms and recovery [123.6 vs. 147.4 hours, respectively, (P = 0.001)].

**Conclusion** Oral folic acid is clinically beneficial for reducing the severity of acute diarrhea in children under five year old. [Paediatr Indones. 2014;54:273-9].

**Keywords:** folic acid, acute diarrhea, duration of diarrhea

**D**iarrhea is defined as an increase in volume or fluidity of stool, changes in consistency, and increased frequency of defecation.<sup>1,2</sup> Acute diarrhea, the most common form of diarrheal illness, has an abrupt onset, usually resolves within 14 days, and may be accompanied by vomiting, nausea, abdominal pain, systemic symptoms, and malnutrition.<sup>3,4</sup>

Diarrhea is a major cause of morbidity and mortality in young children in developing countries, and an important cause of malnutrition. Though the mortality rate for children under five suffering from acute diarrhea has fallen from 4.5 million deaths annually in 1979 to 1.6 million deaths in 2002, acute diarrhea continues to exact a high toll on children in developing countries.<sup>5</sup> Viral pathogens account for approximately 70% of acute infectious diarrhea cases in children, with rotavirus most commonly implicated.<sup>6,7</sup> A two-year prospective case control study in Denmark confirmed rotavirus as the most common pathogenic cause of diarrhea in children under 5 years of age.<sup>8</sup>

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The current management of acute watery diarrhea in infants and children focuses on oral rehydration therapy to correct dehydration and appropriate feeding during and after diarrhea. Since oral rehydration therapy does not reduce the duration of diarrhea, the demand for effective drugs is high, especially in developing countries.<sup>5</sup>

Folic acid has been shown to reduce the severity of acute diarrhea.<sup>9</sup> Rotavirus damages the absorptive cells on the tips of the small intestinal villi, these cells are then replaced with migrating cells from the crypts of Lieberkuhn. Folic acid has a key role in DNA synthesis and assists in epithelial cell renewal of the small bowel mucosa by accelerating the normal generation of damaged cells.<sup>9</sup>

The aim of this study was to assess the effect of folic acid in reducing the severity of acute diarrhea in young children.

## Methods

We conducted a single-blind, randomized controlled trial in Secanggang District, Langkat Regency, North Sumatera Province from August 2009 until January 2010. We included all children aged 6 months to 5 years with acute diarrhea. Children with severe dehydration, cholera, prior consumption of folic acid, and those with critically ill concurrent diseases (severe malnutrition, encephalitis, meningitis, sepsis, bronchopneumonia, or tuberculosis) were excluded. Informed consent was obtained from all parents and this study was approved by the Research Ethics Committee of the University of North Sumatera Medical School.

The WHO defined diarrhea as the passing of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Recovery of diarrhea was defined as a defecation frequency decrease to fewer than 3 times per day, loose or soft stool consistency becoming normal, and stool volume becoming normal (less than 200 ml per day), for 48 hours.<sup>10</sup>

Upon recruitment, subjects underwent standard history-taking and thorough physical examinations performed by a physician. Immediately after admission into the study ward, children were randomized to receive either 5 mg folic acid or placebo at 24-hour intervals for

5 days. There were 56 subjects in each group. Folic acid and placebo were identical in appearance and packaged in identical containers. Subjects were also given rehydration therapy according to WHO guidelines with an oral rehydration solution (ORS).

After admission into the study, subjects' frequency and volume of diarrhea, consistency of feces, and duration of diarrhea were recorded at baseline and after treatment. All children were kept in the study ward for 5 days.

The effect of folic acid and placebo on frequency, volume, and duration of diarrhea were assessed using Student's independent T-test. The effect on consistency of feces was assessed using Chi-square test. Results were considered to be statistically significant for P values < 0.05 with 95% confidence intervals (95%CI).

## Results

One hundred twenty-three children with acute diarrhea visited the clinic. Eleven children were excluded from the study due to severe malnutrition (8 children), severe dehydration (1 child), and parental refusal to participate (2 children). A total of 112 subjects enrolled and were randomly assigned to receive either 5 mg folic acid (n=56) or a placebo (n=56) as a daily single dose for 5 days. (Figure 1)

Baseline characteristics are shown in Table 1. The mean age of subjects in the folic acid and placebo groups were 22.6 months and 25.6 months, respectively. Gender was noted and body weight/body height ratio was measured to assess nutritional status.

Subjects were assessed for severity of acute diarrhea before treatment. There were no statistically significant differences between the folic acid and placebo groups for frequency of diarrhea for the first 24 hours (5.6 vs. 5 times, respectively), volume of feces (72.7 vs. 79.3 mL, respectively), watery consistency (46 vs. 48 subjects, respectively), duration of diarrhea (32 vs. 29.6 hours, respectively), and no dehydration (44 vs. 42 subjects, respectively) (Table 1).

The diarrheal severity in both groups was assessed daily for the 5 days of treatment. Figure 2 shows significant differences in mean daily diarrheal frequency during therapy between the folic acid and

placebo groups starting from the third day of treatment [1.9 vs. 2.8 times per day, respectively, (P= 0.001)] until the fifth day of treatment.

Stool consistency per episode during treatment was also assessed. Beginning at the second day of treatment, less children in folic acid group experienced watery diarrhea compared to those in placebo group,

and it continued to the fifth day of treatment (Table 2).

On the 2<sup>nd</sup> day of treatment, the daily volume of feces was significantly less in the folic acid group than in the placebo group [147.5 vs. 217.5 mL, respectively, (P= 0.001)]. These significant differences continued through the 5<sup>th</sup> day (Figure 3).

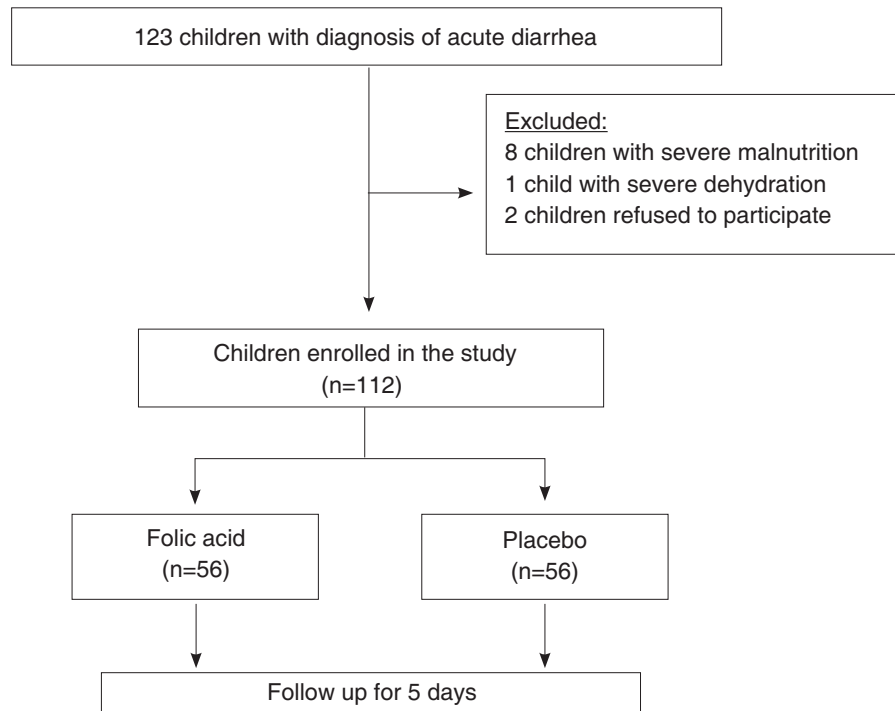


Figure 1. Study flow chart

Table 1. Baseline characteristics of subjects

Characteristics	Folic acid n=56	Placebo n=56
Mean age (SD), months	22.6 (12.14)	25.6 (10.43)
Gender, n (%)		
Male	26 (46.4)	28 (50)
Female	30 (53.6)	28 (50)
Mean BW/BH* ratio (SD)	98.1 (20.21)	96.5 (20.7)
Severity of acute diarrhea		
Mean frequency (SD), times/day	5.6 (2.16)	5 (1.34)
Consistency, n (%)		
- Watery	46 (82.1)	48 (85.7)
- Soft	10 (17.9)	8 (4.3)
Mean volume of feces (SD), mL/episode	72.7(26.46)	79.3 (24.56)
Mean duration of diarrhea (SD), hours	32 (18.44)	29.6 (16.68)
Degree of dehydration, n (%)		
- No dehydration	44 (78.6)	42 (75)
- Mild to moderate dehydration	12 (21.4)	14 (25)

\*BW/BH: body weight/body height

The duration of acute diarrhea was assessed in both groups. We assessed recovery from acute diarrhea in two ways: the time from treatment until recovery and the time from early symptoms until recovery. Duration of acute diarrhea from initial treatment until recovery in the folic acid group was significantly less

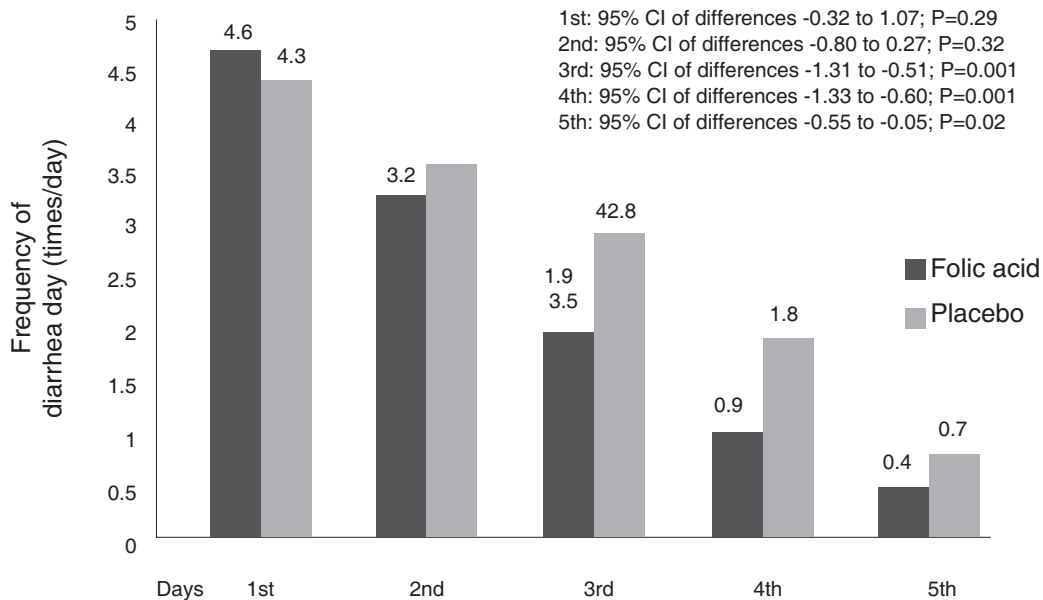
than that of the placebo group [91.3 hours vs. 117.9 hours, respectively, (P=0.001)]. The duration of acute diarrhea from the first day of symptoms until recovery was also significantly less in the folic acid group than the placebo group, with mean recovery times of 123.6 hours vs. 147.4 hours, respectively, (P= 0.001)] (Table 3).

**Table 2.** Consistency of feces during treatment

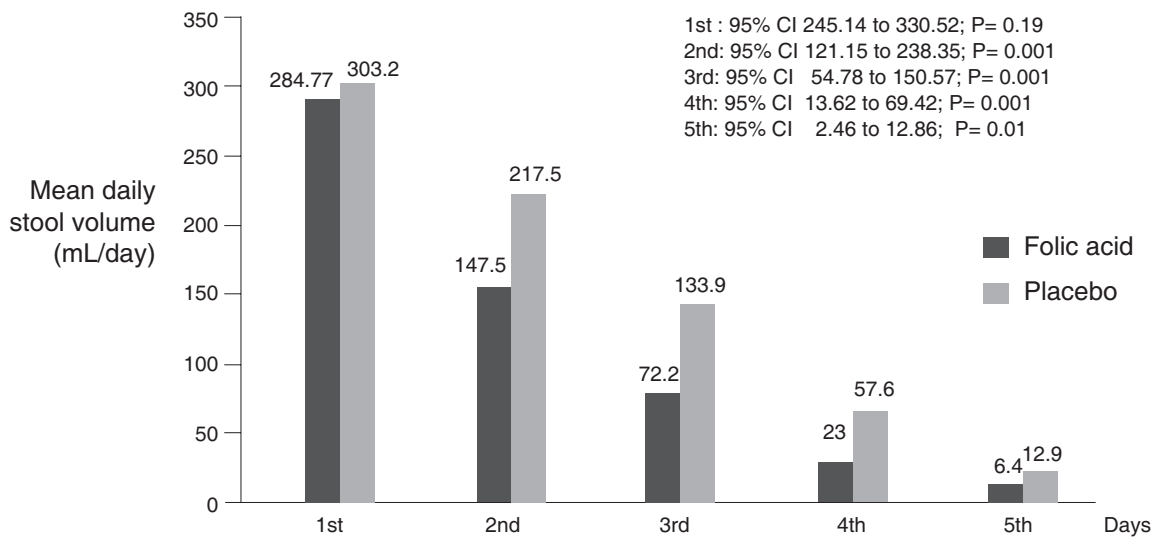
Consistency of feces	Folic acid (n = 56)			Placebo (n = 56)			95% CI of differences	P value
	watery n(%)	soft n(%)	normal n(%)	watery n(%)	soft n(%)	normal n(%)		
1 <sup>st</sup> day	46 (82.1)	10 (17.9)	0	48 (85.7)	8 (14.3)	0	- 0.10 to 0.17	0.59
2 <sup>nd</sup> day	30 (53.6)	25 (44.6)	1 (1.8)	42 (75.0)	14 (25.0)	0	0.03 to 0.43	0.02
3 <sup>rd</sup> day	3 (5.4)	43 (76.8)	10 (17.8)	15 (26.8)	40 (71.4)	1 (1.8)	0.19 to 0.56	0.001
4 <sup>th</sup> day	0	22 (39.3)	34 (60.7)	1 (1.8)	46 (82.1)	9 (16.1)	0.30 to 0.63	0.001
5 <sup>th</sup> day	0	8 (14.3)	48 (85.7)	0	18 (32.1)	38 (67.9)	0.03 to 0.32	0.02

**Table 3.** Duration of acute diarrhea

Mean duration of diarrhea (SD), hours	Folic acid group	Placebo group	95% CI of differences	P value
Initial treatment until recovery	91.3 (24.82)	117.9 (22.08)	-36.50 to-16.64	0.001
Initial symptoms until recovery	123.6 (32.9)	147.4 (33.06)	-38.41 to-9.94	0.001



**Figure 2.** Frequency of diarrhea during treatment



**Figure 3.** Volume of feces during treatment

## Discussion

In this study, we recruited subjects with diarrhea. Subjects' mean diarrheal frequency was 5.3 times in 24 hours, stool consistency was liquid and soft, mean stool volume was 76 mL per episode and mean duration of diarrhea was 30.8 hours. Subjects were children aged 6 to 60 months, with a mean age of 24.1 months. Children younger than 6 months were excluded because many were breastfeeding. Dehydration status was assessed and treated according to *World Health Organization (WHO) 2005 Guidelines*,<sup>11</sup> but most subjects were not dehydrated.

In developing countries, diarrhea is one of the main causes of morbidity and mortality in children younger than 5 years of age, with an average number of episodes of diarrhea per child per year of 3.2.<sup>12</sup> Twenty-one percent of childhood mortality in children younger than 5 years in these countries is associated with diarrhea, resulting in 2.5 million deaths per year.<sup>13</sup>

Lack of breastfeeding, inappropriate rehydration therapy, severe malnutrition, frequent vomiting and diarrhea, low socioeconomic status, and the presence of associated major infections are recognized risk fac-

tors for the development of dehydration in children with diarrhea.<sup>14</sup> However, few studies have systematically assessed the role of specific microorganisms in the etiology of dehydrating diarrhea. Many different pathogens, including bacteria, viruses, and parasites, cause diarrhea.<sup>15,16</sup>

Although we did not identify the microorganisms that caused diarrhea in this study, rotavirus has long been recognized as a leading cause of acute diarrhea in young children throughout developing and developed countries. The peak age for infection is between 6 months and 2 years, and the mode of spread is by the fecal-oral or respiratory route.<sup>17</sup> A study from Lima, Peru (1999) on children under 5 years with diarrhea detected rotavirus in 52% of inpatients and 35% of outpatients [odds ratio (OR) = 2.3%], and 95% of the rotaviruses among the inpatients were serotypes G1-G4.<sup>18</sup> In an outbreak of acute diarrheal disease reported in Kupang, Nusa Tenggara, Indonesia in August 2002, rotavirus was found to be the etiological agent, with serotype 1 predominating.<sup>19</sup> We assumed the leading cause of diarrhea in our study was rotavirus because our subjects were young children aged 6 to 60 months.

Results from a South African study showed that

oral folic acid significantly decreased the duration of acute diarrhea in children.<sup>20</sup> Folic acid, a water soluble vitamin, is a simple, inexpensive treatment, and relatively non-toxic in humans. Experimental work suggests some benefit. In rotavirus infections, the most common cause of severe acute watery diarrhea in children, absorptive cells of the small intestinal villi are damaged and replaced by migrating epithelial cells from the crypts of Lieberkuhn. Folate has a key role in DNA synthesis and assists in the renewal of epithelial cells by accelerating the normal regeneration of damaged cells.<sup>9</sup>

Folate is a generic term for the vitamin that functions coenzymatically in the transfer and processing of the one of the carbon units for the remethylation of homocysteine to generate methionine, the synthesis of thymidylate and purines and the formation of methyl groups needed for many biological methylation reactions.<sup>21</sup> Folate bioavailability in large part is governed by the extent of intestinal absorption. Polyglutamyl folates, which constitute much of naturally-occurring folate in food, must undergo enzymatic deconjugation in the small intestine before absorption. This reaction is catalyzed primarily by a pteroylpolyglutamate hydrolase associated with the jejunal brush border membrane, with possible contribution of hydrolase activity from pancreatic secretions. Absorption of monoglutamyl folate occurs via a saturable transport process in optimally acidic pH. A nonsaturable absorption mechanism also functions when folate concentrations in the intestinal contents exceed 5-10  $\mu\text{mol/L}$ . Because of the existence of two absorption processes, findings regarding folate bioavailability at a certain dosage level may not be predictive of bioavailability at a substantially higher or lower intake.<sup>22</sup> The effectiveness of folic acid for treating diarrhea is unclear. A study in Bangladesh reported that folic acid therapy did not clinically benefit infants and young children with acute watery diarrhea.<sup>23</sup> It is clear from this study that folic acid had a beneficial effect for treatment of acute watery diarrhea in these children aged 6-60 months. The administration of oral folate even in a dose of 3 x 5 mg every day for 5 days reduced the frequency, volume and duration of acute watery diarrhea until they recovered from diarrhea.

There are several possible explanations for our differing results from those of Ashraf *et al.* The Ban-

gladeshi study had male children aged 6-23 months with a history of acute watery diarrhea of less than 72 hours duration with some signs of dehydration. Our study had a different patient population, since our subjects were in the age group of 6 – 60 months, included both male and female patients, and were of different economic and cultural backgrounds. As such, we had a more diverse population group. The discrepancy involving the duration of acute diarrhea may be due to acute watery diarrheal illness usually resolving spontaneously within 7–10 days without treatment.<sup>10</sup> Because the mean duration of diarrhea from the initial symptoms was 5 days in the folate group, folate was observed to shorten the duration of diarrhea.

In conclusion, this study has shown that folic acid given as an adjunct to fluid and electrolyte therapy provides an additional clinical benefit to infants and young children with acute watery diarrhea.

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