FOLIC ACID SUPPLEMENTATION IN THE TREATMENT OF ACUTE WATERY DIARRHEA IN CHILDREN 6 MONTHS TO 36 MONTHS OF AGE: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL

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OBJECTIVE: To determine the efficacy and safety of folic acid supplementation among pediatric patients 6 months to 36 months old with acute, non-bloody diarrhea in Quirino Memorial Medical Center.

STUDY DESIGN: randomized, double- blind placebo-controlled clinical trial

SSETTING: Pediatric Ward of a Tertiary Government Hospital.

PARTICIPANTS: Seventy two subjects aged 6 month to 36 months old with acute non bloody diarrhea of six days duration or less, with some or moderate signs of dehydration based on WHO-CDD protocol.

INTERVENTION: Subjects were randomized into two treatment groups: Group 1 (Folic Acid Group) and Group 2 (Placebo Group)

OUTCOME MEASURES: Efficacy of the folic acid was measured in terms of stool characteristics, frequency, volume and duration

RESULTS: A total of 72 diarrheal cases ages 6 months – 36 months were enrolled to the study. The two groups were essentially similar in terms of age, sex and degree of dehydration. Mean age was 11.3 months for Group 1 and 13 months for Group 2. The character of stool was described as either liquid, semi-formed/semi-liquid, and formed stool. The stools significantly differed in the

two groups by Day 2, 75% of subjects in Group 1 showed semi-formed stool, and 33% in Group 2 (P value – 0.0009). By Day 3, 53% of subjects in Group 1 had formed stools , and only 11% in Group 2. Among the subjects not discharged at days 3 and 4, the proportion of those with formed stools was significantly higher in Group 1 than in Group 2. The volume of stools measured in grams was similar for Day 1 in both groups, but at days 2-3, the volume of stool was significantly lower in Group 1 than in Group 2 (P value 0.0000). It showed that there was a significantly higher proportion and percentage (cumulative) of subjects discharged starting day 3, in Group 1 than in Group 2. By day 5 , 97% of patient in group 1 was discharged while only 75% in group 2. The length of hospital stay was 2.3 days in Group 1 and 3.6 days in Group 2 (P-value 0.0000).

CONCLUSION: Folic acid supplementation to the management of acute diarrhea enabled majority of the subjects in this study to have earlier formed stools, reduce volume of stool earlier and reduce frequency of stooling, resulting in early discharge and shorter hospital stay.

KEYWORDS: acute diarrhea, bloody diarrhea, folic acid, supplemental treatment

INTRODUCTION

Diarrhea remains a leading cause of morbidity and mortality among children less than five years of age around the world.[1] In the year 2000, diarrheal diseases claimed an estimated 1.4 to 2.5 million lives. The incidence and the risk of mortality from diarrheal diseases are greatest among children younger than 1 year of age. The morbidity from diarrhea remained relatively constant during the past two decades, with each child under 5 years of age experiencing an average of three episodes per year. Other direct consequences of diarrhea among children in resource limited countries include malnutrition, diminished growth, and impaired cognitive development.[2]

In the Philippines, diarrhea is one of the ten leading causes of death among children. It's prevalence has not improved in the last five years. In 2003, the National Demographic and Health Survey (NDHS) reported that 11% of the children under five years of age had diarrhea, this figure indicated an increased of 57% from 7% level in the 1998 NDHS data.[3] A slight decreased of 9% was reported in the 2008 NDHS.[4] The 2006 Department of Health Field Service Information System reported that acute watery diarrhea is the second among the ten leading causes of morbidity with the rate of 707.7 per 100,000 population of children under five years of age. Death due to acute diarrhea is usually due to severe dehydration which can be prevented with proper management.[5]

During the past three decades, several factors were noted to have improved the mortality rate of diarrhea, such factors include: widespread distribution and use of oral rehydration solutions (ORS), improved rates of breastfeeding, improved nutrition, better sanitation and hygiene, and increased coverage of measles immunization.[2]

Over the years, supplementation and drugs used for diarrhea were instituted like zinc, multivitamins, minerals, antimotility, and antisecretory agents.[2] Oral rehydration solution (ORS) treatment had reduced significantly the incidence of mortality and morbidity caused by diarrhea but ORS does not shorten the duration, does not change the consistency of stool, and it does not normalize gastrointestinal flora.[6]

The current management of acute diarrhea in infants and children focuses on oral rehydration therapy for the correction of dehydration and appropriate feeding during and after diarrhea.[7]

A randomized controlled trial done in the Philipines by Sanidad R.,MD compared the tolerability between flavored ORS vs unflavored ORS in children. It was found out that unflavored ORS was better tolerated than the flavored ORS preparation among children four months to five years with acute diarrhea having no or some dehydration (P-value 0.05).8

Several studies with zinc as a supplement in the control of diarrheal diseases

were done. A study with zinc along with selected vitamins was done in India which resulted in clinically important reductions in the duration and severity of diarrhea among pre-school age (P-value 0.02).[9] A collaborative study of 5 countries (Brazil, Ethiopia, Egypt, India and the Philippines) was done in 2005. The used of 20 mg zinc tablet dissolved in 5ml water or breastmilk given once daily for 14 days for the treatment of childhood diarrhea resulted in a reduction in the used of other medications without affecting the use of oral rehydration solution (P-value .04).[10]

A study done by Almera-Cirilos, MD at San Juan de Dios Hospital in 2004 with 120 patients 6 months to 36 months old with Acute Diarrhea (P-value .019)[11] and a study by Teodoro-Serillo N.,et al with 150 patients 6 -48 months in 2006 in a Tertiary Government Hospital and Provincial Hospital (P-value 0.000674)[12] showed that administration of zinc had reduced the frequency and consistency of stools in children with acute diarrhea. Zinc was proven to be tolerable and had no side effects[11].

The effect of Vitamin A supplementation on duration of diarrhea was evaluated by Dewan V, et al in India which showed that vitamin A supplementation does not significantly reduced the duration of diarrheal episode. However, this study concluded that children with pre existing vitamin A deficiency particularly those who have associated malnutrition may have beneficial effect (P-value 0.025).[13]

A comparative clinical efficay of Saccharomyces boulardii and yogurt fluid in acute non-bloody Diarrhea in children was done in Turkey. Although, the overall duration of the diarrhea in both groups was not different, normalization of stool composition and frequency was more rapid in the group given Saccharomyces boulardii (P-value <.05).[6]

Probiotic has also been proven to shorten the duration of acute diarrheal illnesses in children less than five years old by approximately one day (P-value <.001)[13] as shown in a meta analysis done by Huang JS in Massachusetts, USA .[14]

Recently, folic acid supplementation in acute nonbloody diarrhea is the subject of several studies. Haffejee in 1988 did a preliminary trial on folic acid supplementation among infants 6 months to 36 months. The study showed favorable results.[15] In 1998, a double blind, randomized controlled trial negated the positive results observed in the Haffejee study.[7] A local study done by Valenzuela and Santos in 2003, concluded that folic acid supplementation is beneficial to patients 6 months to 5 years suffering from acute nonbloody diarrhea (P-value< 0.00001).[16]

The early studies done on folic acid in diarrhea had been controversial. This was followed by a unpublished local study in a private hospital in patients 6 months to 5 years with acute non-bloody diarrhea with no or some signs of dehydration which showed a

good result (P-value < 0.000001).[16] On the other hand, this study was done in a tertiary hospital in 6 months to 36 months old patient with acute watery diarrhea with mild to moderate dehydration.

The objective of this study is to determine the efficacy and safety of folic acid supplementation among pediatric patients 6 months to 36 months old with acute non-bloody diarrhea admitted in a Tertiary Government Hospital. It further aims to compare the effects of folic acid supplementation versus placebo as to: duration of diarrhea; frequency of stool passage; volume and character of stools and to determine the adverse effect of folic acid supplement.

METHODOLOGY

STUDY DESIGN

This is a Randomized, Double-Blind Placebo-Controlled Clinical Trial.

SETTING

This study was conducted at the Pediatric Ward of a Tertiary Government Hospital.

STUDY POPULATION

Included in the study were: Children 6 months to 36 months old with acute non bloody diarrhea of six days duration or less; with some or moderate signs of dehydration based on WHO-CDD protocol.[18]

Excluded in the Study were: Children with diarrhea of more than six days duration with: severe dehydration; bloody diarrhea; previous operation; severe malnutrition; immunocompromised; history of seizure (intake of medications for epilepsy); fecalysis findings of helminthiasis, amoeabiasis, occult blood; and with intake of anti-diarrheal medication.

Sample Size:

Seventy two patients were sampled based on the following assumptions: 95 % Confidence level, 80 % Power, SD of 2 and difference of 2 days duration of diarrhea based on the study of Valenzuela, et al. [16] The sample size for the two groups comparing means was computed with the following formula:

$$n = \frac{(z \times 1-\beta)^2 \times 2 \times SD2}{(d')^2}$$

$$n = \frac{(1.96 \times .84)^2 \times 2 \times SD2}{(2)^2}$$

where:
n = total sample size
z = the standard normal deviation, usually set at 1.96 or more simply

Power = $1 - \beta$ = Probability of rejecting the null hypothesis when it is false
SD = Standard deviation
d' = difference between two samples

Designation of Duties and Responsibilities:

The principal investigator gave a research orientation to the members of the research team prior to the start of the study. Duties and responsibilities were given to each member. A thorough physical examination was done on each patient by a resident physician assigned at the Emergency Room. He/she classified the degree of dehydration according to the WHO/CDD assessment of dehydration. A nurse unknowleadegable of the study objective and treatment assignment administered the Folic acid and the placebo. A Pediatric Resident assigned in the gastroenteritis ward did the daily physical examination and recorded any adverse effect that the children experienced during the treatment.

Treatment Allocation:

The subjects were screened for the exclusion and inclusion criteria through interview of parents and guardians and physical examination of the patients. Name of children with informed consent from parents was included in the list of participants. Subjects were assigned to the 2 treatment groups using a randomization list. Group A was given Drug A (Lot. No. 01) , Group B was given Drug B (Lot. No. 02).

The Folic acid preparation given to each patient was commercially available and provided by a Pharmaceutical Company. Folic acid was repackaged at the University of the Philippines College of Pharmacy, Department of Industrial Pharmacy along with the placebo. The placebo has the same color, taste and odor as that of folic acid and placed in an identical bottle.

Ethical Consideration:

The study was done according to the Principles in the Declaration of Helsinki. Parents of the children were informed about the nature, procedures, benefits and risks related to the study. An informed consent was obtained for their inclusion.

An Assistant Investigator assigned in the gastroitestinal ward noted and recorded any adverse effects. Parents were likewise instructed to report any untoward manifestation to the Assistant Investigator assigned to their ward. The study was approved by Ethics Review Committee.

Randomization:

Random allocation of the subjects to one of two treatment groups was done using pre-drawn block random assignment. The randomization list was prepared using letters A and B. Six 4-letter combinations (which serve as blocks) was made using these 2 letters i.e., ABAB, ABBA, AABB, BABA, BAAB, and BBAA . These 6 combinations became the basis for assigning treatment grouping by substitution with the corresponding number generated from random numbers. The pre-drawn treatment assignments were placed in a sealed envelope.

Definition of Terms

Acute Diarrhea - is the passage of loose or watery stools, at least three times in 24 hours period and may last 2 to5 days.[17]

Dehydration - the amount of fluid loss secondary to diarrhea not replaced adequately. A deficit of water and electrolytes develops.[17]

Tolerability - the ability of the subject to ingest a substance without vomiting.[8]

Actual Conduct of the Study

A physician assigned at the emergency room did the baseline physical examination. He/She classified the degree of dehydration according to the WHO/CDD assessment of dehydration (**Appendix A**). Parents of the subject were informed about the purpose, benefits, and risks related to the study (**Appendix B**). Patient informed consent was obtained prior to their inclusion (**Appendix C**). Once the patient fulfilled the inclusion criteria, he/she was assigned randomnly to either Group A (intravenous fluid and folic acid) or Group B (intravenous fluid and placebo).

A Randomnization list was prepared using letter A for Group A; and letters B for Group B. A total of six (6) combinations of the two (2) letters in random order was formed and was written on separate sheets of paper properly sealed (**Appendix D**). Each random order had an equal chance of being drawn and assigned to each group.

Group A children recieved Folic acid 5ml oral (1mg per 1 ml,equivalent to 5mg) three times a day for 5 days and intravenous fluid. Group B children recieved a placebo 5ml three times a day for 5 days and intravenous fluid. The placebo is of the same color, taste and and appearance. It was kept in a container similar to that of folic acid supplement.

The two assistant investigators who were both blinded evaluated the duration of patient's diarrhea as well as the frequency of stool passage, volume and character of stools (**Appendix E**). Adverse reactions were also observed by the investigators (**Appendix F**). **Figure 1** outline the study procedure.

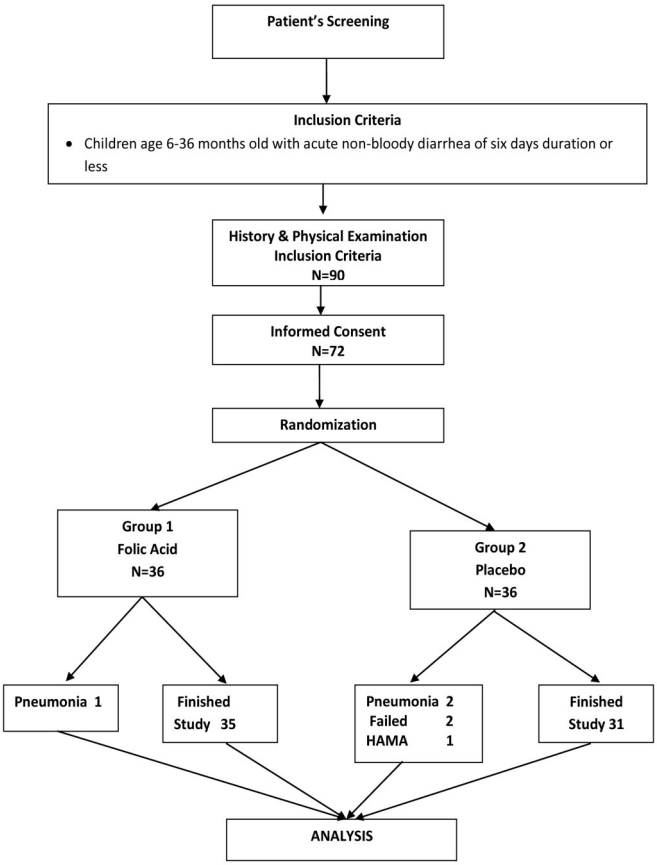

Figure 1: FLOW CHART OF STUDY PROCEDURE

Measures of Outcome

The study outcome measure determined the character, frequency, volume and duration of stool.

The character of stool was determined as follows:

a. Liquid stool – predominantly water.
b. Semi – formed/semi – liquid stool – composed of water and liquid portion.
c. Formed stool – solid stool.

The volume of stool was measured and recorded in grams by weighing the diaper before and after each use. A weighing scale (Silvano Brand - 3 kg) was used and was calibrated every day. The frequency of stool was noted and recorded every 8 hours shift.

Data Analysis

Means and standard deviations, frequency counts and percentage were used to described the data. T-test for independent samples was used to compare continous variables and chi-square and Fischer's exact test for categorical variables. Odds ratio were computed. A 95 % confidence level or P value < 0.05 was considered significant. Minitab ver 16 was used as statistical software.

RESULTS

A total of 90 patients 3 months to 6 months of age qualified to the inclusion criteria. A total of 72 patients gave consent and were randomized to Group A – folic acid (36 patients) and Group B- placebo (36 patients). Out of 36 patients enrolled in Group A, one (1) had Pneumonia and was considered unimproved but completed the medication for 7 days. In Group B ,there were 2 dropouts, one (1) developed Pneumonia and one (1) went home against medical advised (HAMA). Three were considered unimproved who completed the medication for 7 days, one (1) Pneumonia, two (2) had acute gastroenteritis with moderate dehydration.

The two groups were essentially similar in terms of age (P- value 0.239), sex (P-value 0.124) and degree of dehydration (P-value 0.674) on admission. Mean age was 11.3 months for Group 1 and 13 months for Group 2. There was male preponderance for both groups and majority had mild dehydration on admission. The p value was not statistically significant. (See Table 1)

Table 1. Demographic Profile of subjects as to age, sex and degree of dehydration

	Group 1	Group 2	P Value
Age, in months Mean +/SD	11.3+/5.1	13.0+/7.0	0.239
Sex			0.124
Male	22	28	
Female	14	8	
Dehydration			0.674
Mild	34	32	
Moderate	2	4	

The character of stool was described as either liquid, semi-formed/semi-liquid, and formed stool (Table 2). The stools significantly differed in the two groups by hospital day 2 at which time 75% of subjects in Group 1

showed semi-formed stool, and only 33% in Group 2 (P- value 0.0009). In hospital day 3, 53% of subjects in Group 1 had formed stools, and only 11% in Group 2. For remaining subjects not yet discharged at days 3 and 4, the proportion of those with formed stools was significantly higher in Group 1 than in Group 2.

Table 2. Character of Stool in Different Intervals

Character of Stool	Group 1 N (%)	Group 2 N (%)	P value N (%)
Day 1 Liquid Semi-formed Formed	 36 0 0	 36 0 0	--
Day 2 Liquid Semi-formed Formed	 9 (25%) 27 (75%) 0	 24 (67%) 12 (33%) 0	 P- value 0.0009 OR 6.00 95% CI (2.1-16.7)
Day 3 Liquid Semi-formed Formed	 1 16 19 (53%)	 8 24 4 (11%)	0.0000
Day 4 Liquid Semi-formed Formed	 1 3 8 (67%)	 3 17 8 (28%)	0.049
Day 5 Liquid Semi-formed Formed	 1 0 0	 2 5 11	0.158

The volume of stools which was Measured in grams was similar for Day 1 in both groups, at days 2 and 3, the volume of stool was significantly lower in Group 1 than in Group 2. The p-value 0.0000 is statistically significant.

The frequency of stool as shown in table 4 was significantly less in Group 1 as compared in Group 2 for Days 1 to 3 with a P-value 0.036. This is statistically significant.

Table 3. Volume of Stool in Different Intervals

	Group 1 gms.	Group 2 gms.	P value
Day 1 Mean +/SD	608.1+/135.3	620.3 +/142.2	0.714
Day 2 Mean +/SD	383.6+/116.9	494.5+/106.2	0.0000
Day 3 Mean +/SD	355.3+/107.7	402.3+/118.9	0.0000

Table 4. Frequency of Stool in Different Intervals

	Group 1	Group 2	P value
Day 1 Mean +/SD	4.57+/0.81	5.26+/1.05	0.003
Day 2 Mean +/SD	3.0+/0.73	4.06+/1.25	0.0005
Day 3 Mean +/SD	2.7+/0.65	3.5+/1.11	0.036

The duration of diarrhea for both groups was likewise compared. It showed that there was a significantly higher proportion and percentage (cumulative) of subjects discharged starting day 3, in Group 1 than in Group 2 (see Table 5: Fig. 1). By day 5 , 97% of patient in group 1 was already discharged while only 75% in group 2.

Table 5: Cumulative Percentage of Subjects Discharged Per Hospital Day

	Group 1	Group 2	P value
Day 1	0	0	0.0000
Day 2	0	0	
Day 3	24 (67%)	4 (11%)	
Day 4	35 (97%)	19 (53%)	
Day 5	35 (97%)	27 (75%)	

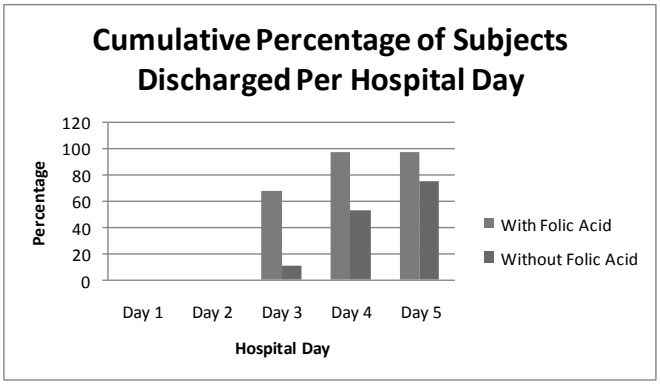

Fig. 1 Cumulative Percentage of Subjects Discharged per hospital day

The Length of hospital stay was 2.3 days in Group 1 and 3.6 days in Group 2. The P value is 0.0000 which is statistically significant.

Table 6 Length of Hospital Stay

	Group 1	Group 2	P value
Mean +/SD	2.3+/0.47	3.6+/1.1	0.0000

Adverse effect

No adverse reaction was noted in the use folic acid.

DISCUSSION

Diarrhea is a common cause of fluid loss in children which can cause dehydration and electrolyte disorders. Most cases can be managed with oral rehydration. Thus, it is important to assess the degree of dehydration, which dictates both the urgency of the situation and the volume of fluid needed for hydration.[18] The outcome of diarrhea range from mild, self-limiting episodes to severe diseases requiring hospitalization.[19] Additional intervention is needed to ensure early recovery and to shorten the course of the disease.

Folic acid supplementation has been shown to have a positive effect in the treatment of acute watery diarrhea in this study. The 2 groups were essentially similar in terms of age (P-value 0.239), sex (P-value 0.124) and degree of dehydration (P-value 0.674). Data on the character of stool showed greater improvement with folic acid supplementation starting day 2 at which time 75% of the subjects in group 1 showed semi formed stool and only 33 % in group 2. The volume of stools was significantly lower in folic acid by day 2 to 3 compared to the placebo group. Frequency of stool was also significantly less in group 1 than in group 2 from day 1 to 3. Comparing the percentage of subject discharged per hospital day there was a significantly higher proportion and percentage

of subjects discharged starting day 3 in group 1 than in group 2. The length of hospital stay was 2.3 days in group 1 and 3.6 days in group 2. The difference was statistically significant. The findings in this study was the same as to age, sex, dehydration to the study done by Valenzuela et al in 2003. However, the mean frequency of LBM/day and the character of stool in the study of Valenzuela started to decreased and improved by day 3 and the volume of stools had no significant difference between the 2 groups.[16]

Folic acid can help repair the damage in lining of the intestine. Folic acid also known as Vitamin 9 or Folacin and folate (the naturally occurring form), are forms of water soluble vitamin B9 which is essential to many body function. It plays a key role in DNA synthesis, which is needed for the regeneration of damaged small-bowel mucosal epithelial cells.[20] Children and adult require folic acid to produce healthy red blood cells and prevent anemia. Folic acid also helps in tissue growth and function. It helps to increase appetite when needed and stimulates the formation of digestive acids and maintains nervous system's integrity and intestinal tract functions. Folic acid is an important nutrient for immune and lymphatic function.[21] It is involved in the production of neurotransmitters such as serotonin, which regulate mood, sleep and appetite.

The data obtained from this study showed beneficial effects of folic acid in acute watery diarrhea. The review of literature revealed that folic acid participates in methylation reactions, it serve as a donor of methyl group to certain substrates involved in metabolic reactions. Two key methylation reactions in which folic acid participates have been identified: The methylation of cobalamin, this substrate then acts as a methyl donor in the interconversion of homocystein and methionine, and the methylation of deoxyuridylate to deoxythymidilate, an important component of cellular DNA and thus would be important in cellular replication and repair. It is this second methylation function of folic acid which is probably responsible for the beneficial effects observed with supplementation in acute diarrheal states.[22]

In the study of Ashraf H, Rahman MM, Fuchs GJ, Mahalanabis D in 1998,[7] the study had shown that folic acid given as adjunct to fluid and electrolyte therapy does not provide any additional clinical benefit to infants and young children with acute watery diarrhea. There were several reasons why these results differ from those of the previous study showing the efficacy of foliate conducted in South Africa.[15] It had a different patient population; they were of different age group (1 to 44 vs 6 to 23 months in the previous and present study), included both male and female patients who were of different socioeconomic and cultural background. Since the previous study was neither randomized nor blind, there was a higher chance of bias in the results. The discrepancy involving the duration of diarrhea between the two studies could be explained as follows: acute diarrheal illness usually resolves spontaneously within 7 to10 days without

treatment. The mean duration of diarrhea prior to admission was 7 days in the previous study, it resolved within 2 to 4 days (in the study and control groups respectively). Similarly, as the mean duration of diarrhea prior to admission was only 2 days in the present study, diarrhea continued beyond 5 days in 40% of the children in both groups.

CONCLUSION

The supplementation of folic acid in the management of acute diarrhea enabled majority of the subjects in this study to have formed stools earlier, reduce volume of stool earlier and reduce frequency of stooling, resulting in early discharge and shorter hospital stay.

The character of stool in this study significantly differed in the two groups by day 2 at which time 75% of subjects in Group 1 (folic acid) showed semi-formed stool, and only 33% in Group 2 (placebo) with a P-value 0.0009. In day 3, 53% of subjects in Group 1 (folic acid) had formed stools, and only 11% in Group 2 (placebo). The frequency of stool was significantly less in Group 1 (folic acid) as compared in Group 2 (placebo) for days 1 to 3 with a P-value of 0.036 which is statistically significant. The lenght of hospital stay was 2.3 days in Group 1 (folic acid) and 3.6 days in Group 2 (placebo). The P.value is 0.0000 which is statistically significant.

There were no reported side effects with folic acid in this study. It is generally tolerated. It maybe taken with or without food.

This study proves that supplementation with folic acid for 5 days with acute watery diarrhea is safe and shortens hospital stay.

RECOMMENDATION

Folic Acid showed importance in cellular DNA synthesis and may help in the repair of the damaged villous cells of the small bowel, making it effective in acute diarrhea. It is recommended to determine its efficacy among infants with chronic diarrhea, infectious diarrhea and intestinal parasitism.

In this study, clinical response to folic acid was assessed during the duration of the subject's hospital stay. It is then recommended that subjects will be evaluated until follow-up as out-patient basis.

APPENDIX A

WHO/CDD

Assessment of Diarrhea patients for Dehydration

	A	B	C
LOOK AT:CONDITION EYES THIRST	Well, alert Normal Drinks normally, not thirsty	Restless, irritable Sunken Thirsty, drinks eagerly	Lethagic Sunken Drinks poorly, or not able to drink
FEEL: Skin Pinch	Goes back slowly	Goes back slowly	Goes back very slowly
DECIDE	The patient has NO SIGNS OF DEHYDRATION	If the patient has two or more signs in B, there is SOME DEHYDRATION	If the patient has two or more signs in C, there is SEVERE DEHYDRATION
TREATMENT	Use treatment Plan A	Weigh the patient if possible, and use Treatment Plan B	Weigh the patient and use Treatment C

APPENDIX B

LETTER TO THE PARENTS

Minamahal na mga magulang,

Ako po si Dr_____, isang residente sa Departamento ng Pediatrics, _____. Nagsasagawa ako ng pag-aaral na "Folic acid in the Treatment on Acute Watery Diarrhea in children 6 months to 36 months: a Double Blind, Randomnized Controlled Trial." Nais kong malaman sa pag-aaral na ito kung ang mga batang bibigyan ng folic acid ay mas mapapadali ang paggaling kumpara sa mga batang walang folic acid.

Ang pagsali sa programang ito ay libre at walang makukuhang pinansyal na bayad.

Bilang mga magulang o taga-pag-alaga, gusto kong ipaalam na magiging bahagi ang inyong anak sa programang ito. Maaaring ang inyong anak ay makakatanggap ng folic acid at maari rin naming hindi. Ang pagpili ng kung sino ang bibigyan ay random na parang pagbunot sa tambiolo.

Magpapapirma ako ng "informed consent" sa inyo bilang patunay na kayo ay sumasang-ayon sa pagsali ng inyong anak sa programa.

Maraming salamat po.

Gumagalang,

_____

Primary Investigator

APPENDIX C

Informed Consent

Katibayan sa Pagpayag

Ako _____, nasa hustong gulang, may asawa, at kasalukuyang naninirahan sa _____
ay nagpapatunay na:

1. Ako ang magulang/ tagapagsubaybay ni _____.

2. Lubos na napaliwanagan tungkol sa kahalagahan at pakay ng pag- aaral na may kinalaman sa epekto ng "folic acid" sa ikabibilis at ikadadali ng paggaling sa sakit na "gastroenteritis" ("pagtatae'). Pati na ang pagsusuri at pamamaraan na kinakailangang gawin. Ako ay sumasang ayon na maisama ang aking anak sa pag aaral na ito.

3. Ang aking anak nay lubos na nasuri at napag alamang may sakit na gastroenteritis ("pagtatae") at walang kaakibat na ibang karamdaman.

4. Ako ay nangangako na magbibigay ng lubos na partisipasyon sa pagtatala ng karakter at dami ng dumi ng aking anak sa loob ng tatlo hanggang limang araw (3-5).

5. Alam ko na ang aking anak ay bibigyan ng "folic acid" 5mg/placebo, tatlong beses (3) sa isang araw, sa loob ng tatlo hanggang limang araw (3-5) na walang kapalit na halaga.

6. Ako ay bibigyan ng kasiguraduhan na lahat ng resulta ng pag-aaral na ito at mananatiling lihim at konpidensyal, na ako ay maaring tumiwalag sa pag aaral na ito sa anumang oras aking naisin.

7. Ako ay may karapatang magtanong ng mga bagay-bagay na may kinalaman sa pag-aaral na ito at ako ay nabigyan ng kasagutan na nagbigay liwanag sa aking kaisipan.

8. Ako ay nabigyan ng kopya ng katibayan na ito.

_____ _____

Magulang/ Tagapagsubaybay Petsa

_____

Pangalan at Lagda ng nagpaliwanag na Doctor

APPENDIX D

Randomization Table

1	A	B	A	B
2	A	B	B	A
3	A	A	B	B
4	B	A	B	A
5	B	A	A	B
6	B	B	A	A

APPENDIX E

Patient Data Form

Name of Patient_____ Age/Sex_____

Date/Time	Character of Stools	Volume of Stools	Frequency of Stools

APPENDIX F

Adverse Reaction Checklist

Name of Patient_____ Age:_____

Date	Vomiting	Abdominal pain	Hypersensitivity reaction	Others

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