

The effect of oral folic acid supplementation on the course of acute infantile diarrhea

Dr. Rajaa Jabbar Kadhum: MBChB, DCH,CABP
Kufa University, college of medicine, pediatric department

Dr.Eman jabbar K. Alghizzi: MBChB,DCM,.MSc microbiology
Kufa University, college of medicine, department of community medicine

الخلاصة:

من اجل بيان مدى فائدة تزويد الأطفال الرضع الذين يعانون من الإسهال الحاد بحامض الفوليك الضروري لاستعادة بناء بطانة الأمعاء بعد تلفها نتيجة لإصابتها بالالتهاب الحاد وذلك للإسراع في شفاء الأطفال الرضع والتقليل من فترة رقودهم في المستشفى الذي بدوره سيقال من الجهد على العائلة والطفل والخدمات الطبية. أجريت الدراسة على 150 طفل تتراوح أعمارهم من 2 - 24 شهر يعانون من الإسهال الحاد . وتم إضافة حامض الفوليك بجرعة 5 ملغم ثلاث مرات يوميا إلى العلاج الذي يتلقاه 75 طفل رضيع تم اختيارهم بصورة عشوائية وترك 75 رضيع بدون استعمال حامض الفوليك للمقارنة . وتمت متابعة الأطفال الرضع خلال فترة رقودهم . كان معدل فترة الرقود في المستشفى للرضع الذين تناولوا عقار الفوليك أسد هو $3,09 \pm 1,38$ يوم ومعدل رقود الرضع الذين لم يتناولوا العقار هو $3,04 \pm 1,14$. لم يكن الفرق بين معدل رقود المجموعتين في المستشفى ذو أهمية لذلك نقترح عدم استعمال الفوليك أسد لهذا الغرض .

Abstract:

To evaluate the effect of folic acid on the course & management of acute infantile diarrhea to decrease the burden on the families & health services, 150 infants aged 2-24 months with history of acute diarrhea of 1-10 days duration were randomly selected from Al-zahraa teaching hospital in Najaf city . 75 patients were received folic acid in a dose of 5mg at 8 hrs intervals in addition to the hospital treatment of acute diarrhea & the other 75 patients did not receive folic acid & left as a control group. The admission characteristics were comparable in both groups. Both groups were followed up during hospitalization for signs of improvement or complications & the period of hospitalization . the mean period of hospitalization $\pm 1SD$ was 3.09 vs. 3.04 days for the folic acid vs. the control group respectively. The findings, therefore, should suggest the prevention of unjustified use of folic acid to shorten the hospitalization period of hospitalized infants with acute diarrhea.

Introduction:

Acute diarrheal diseases are one of the leading causes of mortality & morbidity in children worldwide causing one billion episodes of illness & 3-5 million deaths annually⁽¹⁾. the relative importance & epidemiological characteristics of diarrheal pathogens vary by geographic location^(2, 3, 4), but all children in developed & developing countries acquire Rota virus & many selected cases, other than viral enteropathogens & Giardia Lamblia during the first 5 years of life. The major mechanism of transmission is person to person through fecal oral rout although the pathogens which needs small inoculum size may be transmitted by person to person contact (e.g. shigella, E.coli 0157:H7, enteroviruses, Giardia lamblia, & Entamoeba histolytica). Complications of acute diarrhea include dehydration, secondary disaccharidase deficiency, chronic diarrhea & malnutrition, hemolytic uremic syndrome, reactive arthropathy & acute renal failure⁽¹⁾. Because most of acute diarrheal attacks involve damage to the GIT mucosa; the issue of mucosal

recovery assumes a central importance. since the role of folic acid in cell regeneration & DNA synthesis is established especially in more rapidly regenerating tissues, a role of folic acid as an adjuvant therapy in acute diarrhea has been investigated ^(5, 6). one study concluded the presence of a positive difference in the duration of illness in patients receiving oral folate during their illness, the study recommended the use of folic acid in acute diarrheal attacks ⁽⁵⁾. A later study on the same subject found no significant difference to justify routine use of folic acid in acute diarrhea, & recommended discontinuation of this practice ⁽⁶⁾. Folic acid is an essential B vitamin that is not produced by the animal cells because of the inability of the cell to conjugate para-aminobenzoic acid (PABA) & pteridine ring, the two parts of the folic acid molecule. It must be converted into the active 5-methyltetrahydrofolate to be used by the tissues. folic acid is abundantly available in yeasts, leafy green vegetables & animal liver ⁽⁷⁾. but as a polyglutamate molecule These cannot be absorbed until deconjugated by the brush border enzyme folate conjugase (hydrolase) to a monoglutamate form & is either methylated or formulated to enter the portal circulation ⁽⁸⁾. folate are key coenzymes in nucleic acid synthesis DNA&RNA & in amino acid metabolism. deficiency results from low intake, decreased absorption, or increased demand as in pregnancy. deficiency results in megaloblastic anemia with hyper segmentation of neutrophils due to delayed bone marrow maturation of nuclear elements of stem cells ⁽⁹⁾. specifically on the intestinal mucosa folic acid deficiency was associated with distortion of the intestinal morphology ⁽¹⁰⁾. Megaloblastic changes of crypt cells, & increased crypt depth with no significant impact on intestinal function ^(10, 11).

Because of the effect of folic acid on the intestinal mucosa & its role in rapid cell regeneration & because of the limited value of specific therapy in the majority of cases of acute diarrhea & the importance of supportive therapies in this majority its reasonable as well as valuable to evaluate the significance of such use of folic acid on the context of the general lines of management of acute diarrhea adopted by most pediatricians working at Al-Zahraa pediatric & maternity hospital

Patients & methods:-

A comparative randomized clinical trial was done on 150 infants (2 months -2 years) admitted to AL-Zahraa hospital in Najaf city for the management of acute diarrheal attacks (duration of diarrhea less than 2 weeks). gender distribution was 85 males & 65 females. Patients who were considered unhealthy prior to their current illness were not enrolled. 75 randomly selected infants received folic acid treatment with their other therapies right from the start of hospitalization they were considered as the treatment group A. the remaining 75 infants were left as Control group & designed as group B. Folic acid treatment was given to group A as sachets containing powdered tablets of folic acid in a dose of 5mg per sachet, given orally three times daily. For each infant data recorded including name, age, sex, weight, address, duration of diarrhea prior to admission, type of feeding, type of diarrheal motion (mucous, bloody, watery), associated signs, complications if present (as dehydration, vomiting, fever) treatment received, results of the general stool examination, markers of severity (times & amount of motions). Both groups were followed up daily during hospitalization, by severity markers, days of hospitalizations, duration of diarrhea & for group A duration of folic acid therapy. Because all patients included in the trial were discharged immediately following clinical improvement, the day of discharge was considered the day to mark the end of the clinical course & stopping folic acid therapy. Criteria for discharge including freedom from diarrhea, vomiting, fever & complications. All patients except four of group A were receiving antimicrobial therapies & this was not interrupted during the follow up. The statistical method used to analyze data is the 95% confidence interval (C.I.) (P-value=0.05) for the difference between the means of control & treatment groups distributions ⁽¹²⁾. If this C.I. includes the zero difference it would be interfered that there is

no statistically significant difference present& vice versa. The statistical test used to determine the 95% C.I. is the S.D. of the differences between the two means SD (d). This C.I. should exclude the zero difference to infer as statistical significance to the differences between the 2 means. The p-value is obtained from the Z score. This p-value must be less than 0.05 to infer a statistical significance to the differences.

Results:

the study was done on 150 infants ,grouped into two groups with mean ages of 10.2 & 10.3 months for group A & group B respectively which had no significant difference (see table1).Before admission the mean durations of diarrhea were 3.9 & 3.8 days for group A & B respectively which has insignificant statistical difference .Mean periods of hospitalization were 3.09 & 3.04 days for group A & B respectively which has statistically insignificant difference & the mean periods of the total durations of diarrhea were 6.9 & 6.8 days for group A & B respectively which also have insignificant difference (table2).The patients were also subcategorized to study the effect of folic acid in relation to such variables as age group(see table1), indicators of severity (see table3), different findings on general stool examinations(see table 4) ,& type of feeding (see table 5). No statistically significant differences were found in the overall as well as the subcategory means periods of hospitalization between infants receiving folic acid & infants with no folic acid treatment .this was at a 95% significance level (p-value 0.05).

Table 1. Periods of hospitalization (admissions) in relation to age groups.

Age (months)	Group A		Group B		p-value	total
	N	Mean admission (days)	N	Mean Admission (days)		N
	(%)		(%)			(%)
2 – 6	18 (24)	2.8	20 (26.7)	2.8	1	38 (25.3)
7 - 12	37 (49.3)	3.2	35 (46.7)	3.2	1	72 (48)
13 - 24	20 (26.7)	3	23 (30)	3.1	0.74	43 (28.6)
Mean age (months)	10.2		10.3		0.91	10.25

Table 2. Mean duration of diarrhea before & during hospital admission.

period	Group A	Group B	p- value
Before admission	3.9	3.77	0.79
Admission days	3.09	3.04	0.81
Total diarrhea days	6.9	6.8	0.83

Table 3. Periods of hospitalization (admissions) in relation to markers of severity.

Severity marker	Group A		Group B		p-value
	N (%)	Mean period of admission (days)	N (%)	Mean period of admission (days)	
Bowel motions more than 10 x per day	29 (38.7)	3.7	30 (40)	3.3	0.24
Bowel motions less than 10 x per day	46 (61)	2.8	45 (60)	2.9	0.72
Large amount of stool	58 (77.3)	3.6	60 (80)	3.5	0.67

Table 4. Periods of hospitalization in relation to general stool examination findings.

Findings on GSE	Group A		Group B		p-value
	N (%)	Mean period of admission (days)	N (%)	Mean period of admission (days)	
Pus cells	19 (25.3)	2.8	16 (21.3)	3.3	0.22
Red blood cells	7 (9.3)	3.1	12 (16)	3.5	0.19
Parasites	8 (10.7)	2.9	9 (12)	3.3	0.42
Normal findings	53 (70.7)	3.2	50 (66.7)	3	0.44

Table 5. Mean periods of hospitalization in relation to the type of feeding.

Type Of feeding	Group A		Group B		p-value
	N (%)	Mean periods of admission (days)	N (%)	Mean periods of admission (days)	
Breast milk only	16 (21.3)	3.2	9 (12)	2.7	0.29
Formula milk only	13 (17.3)	2.6	9 (12)	3.3	0.13
Mixed (breast milk & formula) no added solids	3 (4)	-	6 (8)	-	-
Milk with added solids	31 (41.3)	3.5	37 (49.3)	3.2	0.36
Solids only	12 (16)	2.4	12 (16)	2.8	0.29

Discussion;

Acute infantile diarrhea can cause damage to the lining of the intestine. Folic acid can aid in the process of intestinal lining repair & regeneration.

In one preliminary trial, supplementation of children with acute diarrhea with very high amount of folic acid (5mg t.i.d.) for several days has shortened the duration of acute infectious diarrhea by 42% ⁽⁵⁾ however, a later double- blind, controlled randomized trial failed to show any positive effect with the same dose of folic acid ⁽⁶⁾. our study was done to test the effect of folic acid in a practice environments that represents the general management line adopted in Al-Zahraa hospital. This implies that folic acid is neither the sole nor the major therapy given to the patients with acute diarrhea .in fact 148 of the 150 infants enrolled were receiving full dose of antimicrobial &\or antiparasitic drugs according to the clinical judgment of the treating pediatrician. This may well affect the course &\or duration of hospitalization. As shown in results no significant differences in hospitalization periods were observed between the two groups. it must be noted, however, that this study cannot be meaningfully compared to the previous related trials because of the treatment given to almost all of the patients in this study on one hand, & on the other hand, Ashraf et al ⁽⁵⁾ performed their study on patients selectively having watery diarrhea of less than 3 days duration; our study included all types of diarrhea whether watery, mucous or bloody & of durations ranging from 1-10 days. Since acute diarrheal attacks may differ in their effect on intestinal mucosa, certain variables were taken into consideration & assumed to have a possibly variable impact on the intestinal lining such as the presence of leukocytes & red blood cells on stool samples, both of which are reflective of a more invasive pathogens associated with colitis ⁽¹⁾. however, neither was associated with a significant differences between the two groups. Patients with stool sample positive for parasites were also tested separately for significant difference but were likewise negative. A weak point in the testing of the latter three categories of infants is the relatively small sample sizes, which certainly have a negative effect on the credibility of the statistical inference based on these small samples. The infants enrolled have four major types of feeding tested for difference but all four groups have no such significant hospitalization period difference from their corresponding other group members .again , each category contained a relatively small number of members ,negatively affecting the significance of the test itself.

Although infants of the treatment group with less than 10x bowel motions per day have a significantly shorter mean period of hospitalization than those with more frequent daily motions (p-value<0.01) ,neither the less frequent motion infants nor the more frequent ones differ significantly from their control counterparts..This strongly suggests that hospitalization period is much less affected by folate supplementation than by other aspects of other lines. The following may be considered out to provide a reasonable explanation of the results observed:

- 1- if we consider that the latest study done over the subject have supportive results ⁽⁶⁾ ,the role of folic acid in intestinal pathology during acute diarrhea is not likely a key role .this is either because folic acid is not significantly depleted from the regenerating tissue after damage to the lining as to impede regeneration, or because the supplied folate may not significantly&\or quickly enough replenish the presumed folate deficiency at the cellular level . It should be noted that true pathological changes to the enterocyte due to folate deficiency are late & functionally insignificant ⁽¹¹⁾.
- 2-in considering the earlier study with positive results ⁽⁵⁾ ,it should be noted that our sample represents only patients with acute infantile diarrhea that needed hospitalization . In addition to the fact that these comprise the smaller portion of all infants with acute diarrhea, their admission to the hospital implies a considerable level of severity & complications necessitating this admission. These same factors may well trivialize further the role of folic acid in these patient's management plans. Treatment of hospitalized infants at least here in Najaf, considerably differs from an outpatient-based approach having more tendencies towards conservativeness. Therefore,

we may still assume that testing the effect of folate supplementation on acute diarrhea affecting the majority of outpatient treated infants can be of value.

Conclusions & recommendations

The results of this study showed clearly that there is no significant effect of supplying folic acid to hospitalized infants with acute diarrhea on the duration of hospitalization .the recommendation of supplying folic acid for the purpose of shortening hospitalization is, therefore, not justified. The results, however, do not rule out an effect of such supplementation on infants with acute diarrhea treated supportively on an outpatient bases, nor do they affect the decision to supply folic acid for reasons other than shortening hospitalization period. Since the issue of the role of folic acid in the management of acuter diarrhea is both theoretically reasonable & practically supported by an existing study ⁽⁵⁾ ,it is recommended that the larger proportion of patients with acute diarrhea treated on an outpatient bases be addressed in a carefully controlled study.

References:

- 1-peckering LK, Snyder JD : gastroenteritis in Behman RE , Kleigman AM ,Jenson HB(editors):Nelson Textbook of pediatrics,17th ed.,Philadelphia,Saunders,2004,pp 1272-1277.
- 2- Medeiros MIC , Neme SN,da Silva P , Capuano DM , Errera MC , Fernandes SA, Valle GR , de Avila FA : Etiology of acute diarrhea among children in Ribeirao Preto -SP, Brazil. Rev. Inst. Trop.S.paulo 43 (1):21-24 Jan.-Feb.,2001.
- 3- Branes GL , Uren E , Steven KB ,Bishop RF: etiology of acute GE in hospitalized children in Melbourne , Australia from April 1980 – March 1993.journal of clinical microbiology, January 1998,p.133-138, vol.36 ,N1.
- 4- Torres ME , Pirez MC , Scholetto F,Varela G , Paradi V, Anende F,:Etiology of childhood diarrhea in Montevideo , Uruguay : associated pathogens & unusual isolates. j Clinical microbial. 2001 June: 39 :2134-2139.
- 5-Haffejee IE ; effect of oral folate on duration of acute infantile diarrhea . Lancet, 1988 Aug.6;2:334-335(letter).
- 6- Ashraf H, Rahman MM ,Fuchs GJ: folic acid in the treatment of acute watery diarrhea in children ; a double blind , randomized, controlled trial. Acta Pediatr. 1998;87:1113-1115.
- 7- King MW: the biochemistry Page :vitamins & co-enzymes.an internet brochure.
- 8- Brouwer IA, Van Dusseldrop M,WestCE, Steegers- Theunissen RPM: bioavailability & inefficiency of folic acid in man. Nutrition research review , 14,267-293.
- 9- Hugdon J , Shane B : folic acid in micronutrient research for optimum health , Oregon state university. copyright 2004.an internet bulletin.
- 10- Garcia-Carega M , kerner JA: malabsorptive disorders in Behrman RE , Kleigman RM ,Jenson HB (editors): nelson textbook of pediatrics ,17th ed. Philadelphia ,Saunders,2004,PP 1257-1272.
- 11-Klipstein FA,Lipton SD, Shenck EA: folate deficiency of the intestinal mucosa , the American Journal of clinical nutrition 26:july 1973,pp728-737.
- 12- Farley TMM: basic statistical methods in reproductive medicine .special programme of research ,development & research training in human reproduction.WHO,1211 Geneva ,Switzerland. an internet publication.