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ORIGINAL ARTICLE

Effectiveness of folic acid supplementation in acute watery diarrhea among children under 5 years of age.

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ABSTRACT… Objective: To compare the mean duration of diarrhea among children diagnosed with acute watery diarrhea and treated with folic acid versus placebo in addition to standard treatment. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Pediatric Medicine, Allama Iqbal Memorial Teaching Hospital, Sialkot. **Period:** Oct 2025 to March 2026. **Methods:** 82 children aged 2 months to 5 years who were diagnosed with acute watery diarrhea as per operational definition and met the inclusion criteria and presented to the Department of Pediatric Medicine at Allama Iqbal Memorial Teaching Hospital Sialkot were included in this study. **Results:** The median age was 32 years (IQR: 20.5-51) in the folic acid group and 32 years (IQR: 14.5–45) in the placebo group. Mann–Whitney U test demonstrated a statistically insignificant difference between the two groups (p = 0.278). There were 24 (58.5%) male and 17 (41.5%) females found in Group A while 23 (56.1%) male and 18 (43.9%) females in Group B. The comparison of duration of diarrhea showed significant difference between both groups p-value 0.016. **Conclusion:** This study demonstrates that folic acid provides no additional therapeutic advantages to babies and young children suffering from acute watery diarrhea when given with hydration and electrolyte therapy. This information should assist healthcare providers and doctors in averting the unwarranted use of folate in the management of acute watery diarrhea in children.

Key words: Acute Watery Diarrhea, Children, Folic Acid, Supplementation.

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INTRODUCTION

Diarrhea is one of the leading causes of morbidity and mortality in children less than 5 years of age which is caused by a variety of bacterial, viral or parasitic organisms, most common of which are viruses.[1] Diarrheal diseases are responsible for causing over 1.5 billion episodes and 2 million deaths in children annually.[2] This high incidence of diarrhea is due to the lack of access to safe water, younger maternal age, lack of breastfeeding and delay in seeking medical care.[3] The existing management of acute watery diarrhea emphases on oral rehydration therapy (ORS) to correct the hydration status of the patient which is safe, cost-effective, easily available as well as life-saving.[4] However, in underdeveloped countries, the correct rehydration therapies are not given due to inadequate education and understanding of caregivers regarding the preparation and administration of fluids, leading to a higher number of deaths from diarrhea and dehydration.[5]

Therefore, any drug that would reduce the duration of disease or frequency of bowel movement would be useful in addition to ORT. A large number of drugs have been studied for their role in reducing duration of watery diarrhea and include zinc, probiotics, dioctahedral smectite, racecadotril and oral immunoglobulins of bovine origin but none of these are routinely recommended due to their possible side effects, high cost, or non-palatable taste.[6,7] Folic acid is a water-soluble B vitamin that is synthetically produced and found in fortified foods and nutritional supplements. It is essential for the production and repair of DNA and RNA, as well as the metabolism of amino acids required for cellular division.[8] Intestinal mucosal damage is prevalent in most episodes of diarrhea; hence, the role of folic acid has been investigated as an adjunct treatment for diarrhea, given its crucial function in DNA synthesis, particularly in rapidly proliferating cells.

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Amelia et al, compared the outcomes of folic acid supplementation versus placebo in their randomized controlled trial. Mean age of participants treated with folic acid was 22.6 ± 12.14 months while mean age of participants in placebo group was 25.6 ± 10.43 months. In folic acid group, 46.4% patients were males while in placebo group 50% patients were males. They reported that there was significant difference between folic acid and placebo groups with regards to duration of acute diarrhea (123.6 ± 32.9 vs. 147.4 ± 33.06 hours).[9] However, other studies have proved that there is no such effect of folic acid. Ashraf et al, compared the outcomes of folic acid supplementation versus placebo in their randomized controlled trial. Mean age of participants treated with folic acid was 9.4 ± 2.8 months while mean age of participants in placebo group was 10.8 ± 3.5 months. They reported that there was no significant difference between folic acid and placebo groups with regards to duration of acute diarrhea (108 ± 68 versus 103 ± 53 hours).[10]

Diarrhea is a highly prevalent condition and one of the leading causes of death in local population. It is evident from literature that there exists controversy regarding efficacy of folic acid supplementation in acute watery diarrhea.[9,10]

Rationale of our study was to address this controversy and bridge the gap of scarcity of literature on folic acid supplementation in acute watery diarrhea. While most drugs claim to decrease the frequency of diarrhea, they are expensive and not widely recommended. Folic acid is a cheap and readily available drug which, if proved to be effective in acute watery diarrhea, will reduce the duration of illness and requirement of intravenous hydration hence resulting in improved outcomes and reduced burden on healthcare resources.

METHODS

This randomized controlled trial was conducted at the department of Pediatric Medicine, Allama Iqbal Memorial Teaching Hospital, Sialkot from Oct 2025 to March 2026. Sample size was calculated using WHO Sample Size Calculator by taking Level of Significance as 5%, Power of Test as 90%, with expected mean duration of diarrhea in folic acid group as 123.6 ± 32.9 hours and in placebo group as 147.4 ± 33.06 hours, then calculated sample size came out to be as n = 82 (41 in each group).[9] Non-probability, consecutive sampling technique was used to enroll patients.

Children of both sexes aged 2 months to 5 years diagnosed with acute watery diarrhea according to the operational criteria were included in this research. Duration of diarrhea less than 7 days was considered for eligibility criteria.

Exclusion criteria was considered as severely malnourished children (weight for height z-score < - 3 SD). Children with history of bloody diarrhea. Individuals who have ingested folic acid in the preceding 14 days. Children diagnosed with hospital-acquired diarrhea (diarrhea manifesting after 48 hours of hospitalization) or antibiotic-associated diarrhea. Existence of other comorbidities such as pneumonia, sepsis, meningitis, etc.

OPERATIONAL DEFINITIONS

Acute Watery Diarrhea

Diagnosed based on the occurrence of three or more loose or liquid stools during the preceding 24 hours.[4]

Duration of Diarrhea

It was defined in terms of time duration (in hours) between initiation of treatment and resolution of diarrhea.

The definition of diarrhea resolution was the passage of a minimum of two soft stools or the absence of feces for a minimum of two consecutive 8-hour periods.[10]

Data Collection Procedure

Following approval from the Research Department of CPSP, Pakistan and the Institutional Review Board of Khawaja Muhammad Safdar Medical College (61/REC/KMSMC), 82 children who met the inclusion criteria and were presenting at the Department of Pediatric Medicine at Allama Iqbal Memorial Teaching Hospital Sialkot were enrolled in this study. After a comprehensive explanation of the study's details, the parents/guardians of all participants were required to provide informed

written consent. Baseline demographic and clinical information including age, gender, weight, duration of symptoms, residential status, maternal education and socioeconomic status were recorded on a predesigned form. After inclusion, patients with odd case numbers were included in Group A, while patients with even case numbers were included in Group B. In Group A, children under the age of one received 0.1ml (90 mcg) of L-methyl folate calcium, while those over the age of one received 0.15ml (150 mcg). The placebo for children in Group B was an equal volume of distilled water, with 0.1 ml administered to those under the age of one and 0.15 ml to those over the age of one. The treatment protocol included breastfeeding, dietary guidance, a rehydration strategy, oral rehydration therapy using low osmolarity ORS or intravenous rehydration if required, and zinc sulfate provided per WHO recommendations to all patients in both cohorts. Drug or placebo was given by 1cc syringe orally once a day and patients were followed up in outpatient department daily till resolution of diarrhea. Duration of diarrhea was recorded as per operational definition.

Data Analysis Procedure

Data was entered and analyzed by using SPSS version 30.0. The normality of the quantitative variables was tested by the Shapiro-Wilk's test. Mean ± SD'/ Median with IQR as appropriate was calculated for age, weight, duration of symptoms and duration of diarrhea. Frequency and percentages were calculated for gender, residential status, maternal education and socioeconomic status. Comparison of mean duration of diarrhea in folic acid and placebo group was done using unpaired t-test taking p = ≤ 0.05 as statistically significant. Non-parametric tests were implemented due to the non-normal distribution of the data. Structural variables, such as gender, age, and duration of symptoms, were manageable through stratification. The Mann–Whitney U test and the Chi-square test were implemented as necessary for post-stratification analysis. The statistical significance of a p-value was determined to be ≤0.05.

RESULTS

The median age was 32 years (IQR: 20.5-51) in the folic acid group and 32 years (IQR: 14.5–45) in the placebo group. Mann–Whitney U test demonstrated a statistically insignificant difference between the two groups (p = 0.278). There were 24 (58.5%) male and 17 (41.5%) females found in Group A while 23 (56.1%) male and 18 (43.9%) females in Group B. The comparison of weight and duration of symptoms showed insignificant difference between both groups i.e., p-value 0.812 and 0.503. The comparison of duration of diarrhea showed significant difference between both groups p-value 0.016. (Table-I)

In this study there were 11 (26.8%) urban and 30 (73.2%) rural patients were enrolled in Group A while 15 (36.6%) urban and 26 (63.4%) rural patients were found in Group B. The comparison of socioeconomic status and mother education showed insignificant results p-value 0.806 and 0.924 respectively. (Table-II)

The stratification of age in both study groups showed insignificant results p-value 0.386. (Table-III)

The stratification of gender in both study groups showed insignificant p-value 1.00. (Table-IV)

TABLE-I

Comparison of demographic and clinical variables

		Folic Acid (Group A)	Placebo (Group B)	P-Value
Age (Median IQR) Months		32 (20.5 – 51)	32 (14.5 – 45)	0.278
Gender	Male	24 (58.5%)	23 (56.1%)	0.823
	Female	17 (41.5%)	18 (43.9%)	
Weight (kg) (Mean ± S.D)		14.00 (10.5-15)	14.00 (11-16)	0.812
Duration of Symptoms (Hours) (Mean ± S.D)		70 (58-92)	70 (47-81.5)	0.503
Duration of Diarrhea (Hours) (Mean ± S.D)		30 (25-32.5)	30 (29-37)	0.016

TABLE-II

Comparison of socio-demographic characteristics

		Group A	Group B	P-Value
Residential Status	Urban	11 (26.8%)	15 (36.6%)	0.342
	Rural	30 (73.2%)	26 (63.4%)	
Socioeconomic Status	Low	29 (70.7%)	30 (73.2%)	0.806
	Middle	12 (29.3%)	11 (26.8%)	
Mother Education	Primary	35 (85.4%)	34 (82.9%)	0.924
	Secondary	3 (7.3%)	4 (9.8%)	
	Tertiary	3 (7.3%)	3 (7.3%)	

TABLE-III

Stratification of age in both study groups

Age Groups	Group A	Group B	P-Value
2-11 Months	5 (12.2%)	8 (19.5%)	0.386
12-21Months	6 (14.6%)	7 (17.7%)	
22-31 Months	9 (22%)	5 (12.2%)	
32-41 Months	3 (7.3%)	8 (19.5%)	
42-51 Months	8 (19.5%)	7 (17.7%)	
52-60 Months	10 (24.4%)	6 (14.6%)	

TABLE-IV

Stratification of gender in both study groups

Male	Folic Acid	24 (58.5%)	Mann Whitney U 276	1.00
	Placebo	23 (56.1%)		
Female	Folic Acid	17 (41.5%)	Mann Whitney U 276	1.00
	Placebo	18 (43.9%)		

DISCUSSIONS

Dehydration and electrolyte imbalances are potential consequences of diarrhea, which is a common cause of fluid loss in children. Oral rehydration therapy may be successful in treating the majority of cases. Consequently, it is imperative to assess the severity of dehydration, as this informs the urgency of the situation and the quantity of fluids necessary for rehydration.[11] The repercussions of gastroenteritis are diverse, ranging from minor, self-resolving episodes to severe conditions that require hospitalization.[12] In order to expedite the rehabilitation process and shorten the illness's duration, further intervention is required.

In underdeveloped nations, diarrhea is a primary contributor to illness and death in children under five years old, with an average incidence of 3.2 episodes per child per year.[13] Diarrhea is responsible for 21 percent of the juvenile mortality rate in children under the age of five in these countries, resulting in 2.5 million fatalities annually.[14]

Folic acid may facilitate the healing of damage to the intestinal lining. Folic acid, commonly referred to as Vitamin B9, Folacin, and folate (the naturally occurring variant), is a water-soluble vitamin crucial for several bodily functions. It is essential for the synthesis of DNA, which is required for the regeneration of injured small-bowel mucosal epithelial cells.[15] Folic acid is essential for the production of healthy red blood cells and the prevention of anemia in both children and adults. Folic acid is essential for the development and proper functioning of tissues. It enhances hunger when necessary, increases the production of digestive acids, and preserves the integrity of the neurological system and the activities of the intestinal tract. Folic acid is an

essential vitamin for the proper functioning of the lymphatic and immune systems.[16] It is involved in the synthesis of neurotransmitters such as serotonin, which are responsible for regulating mood, sleep, and appetite.

The evidence from numerous trials suggested that folic acid has advantageous effects in the treatment of acute watery diarrhea. According to the literature review, folic acid functions as a methyl group donor to specific substrates in metabolic processes, participating in methylation reactions. We have identified two primary methylation processes that involve folic acid: The methylation of cobalamin serves as a methyl donor in the conversion of homocysteine to methionine and in the methylation of deoxyuridylate to deoxythymidylate, a critical component of cellular DNA. Consequently, it plays a significant role in cellular replication and repair. The secondary methylation action of folic acid is likely accountable for the advantageous benefits seen with supplementation during acute diarrheal conditions.[17-18]

In this study the median age was 32 years (IQR: 20.5-51) in the folic acid group and 32 years (IQR: 14.5–45) in the placebo group. Mann–Whitney U test demonstrated a statistically insignificant difference between the two groups (p = 0.278). There were 24 (58.5%) male and 17 (41.5%) females found in Group A while 23 (56.1%) male and 18 (43.9%) females in Group B. The comparison of weight and duration of symptoms showed insignificant difference between both groups i.e., p-value 0.812 and 0.503. The duration of gastroenteritis differed significantly between the two groups (p-value 0.016). This research indicates that folic acid did not have any therapeutic advantage in the management of acute watery diarrhea in children aged 2 to 60 months. Oral folate supplementation reduced the duration of acute watery diarrhea. The effectiveness of folic acid in treating diarrhea is still ambiguous. A research in Bangladesh revealed that folic acid treatment offered no therapeutic advantages to newborns and young children suffering from severe watery diarrhea.

CONCLUSION

This study demonstrates that folic acid provides no additional therapeutic advantages to babies and young children suffering from acute watery diarrhea when given with hydration and electrolyte therapy. This information should assist healthcare providers and doctors in averting the unwarranted use of folate in the management of acute watery diarrhea in children.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Arbab Fatima:** Conceptualization, methodology, writing draft.
2	**Mudassar Hussain:** Supervision, data curation.
3	**Hadeeqa Abbas:** Formal analysis, data curation.
4	**Zarghoona Arshad:** Methodology.
5	**Anam Fatima:** Investigation.
6	**Aqsa Mubashar:** Data analysis.