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Brief Report

THE EFFECT OF FOLIC ACID SUPPLEMENTATION IN BETA-THALASSEMIA MAJOR: A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL

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Folic acid is a coenzyme for many important biochemical reactions including synthesis of purines, pyrimidines, and nucleoproteins. The recommended daily allowance of folic acid is 65 – 200 µg/day for infants and children. The recommended dose for deficiency states is 1000 µg/day; the effects of excess amounts of folic acid are unknown. The role of folic acid in preventing progression of arteriosclerosis is rather a new issue. Thrombotic events related to slightly elevated levels of homocystein in adults may be decreased by daily consumption of 1 mg of folic acid together with 5 – 100 mg of pyridoxine.

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Introduction

Folic acid deficiency results in complications such as anorexia, growth failure, increased susceptibility to infections, and gastrointestinal disorders. However, megaloblastic anemia is the best known side effect of folic acid deficiency.[1, 2] Some conditions such as prematurity, pregnancy, lactation, chronic liver diseases, severe infections, chronic and severe hemolysis, and administration of some drugs are mentioned as risk factors for this vitamin deficiency. Nutritional sources are usually enough, as folic acid is found ubiquitously in most vegetables.[1, 2]

Undertransfused patients with β-thalassemia major may need more folic acid as they continue to have ineffective erythropoiesis.[3–5] Recent treatment protocols[6] do not say anything about folic acid supplementation for patients with thalassemia, because it is supposed that regular blood transfusions prevent bone marrow hyper functioning.

As microcytosis of thalassemia major may mask the hematologic hallmark of folic acid deficiency, i.e., megaloblastic anemia, and since blood tests for folic acid are not routinely available, folic acid deficiency may simply be ignored and the patient may suffer from other complications of folic acid deficiency.

A recent study showed that folic acid deficiency is common and severe in our thalassemia major patients. In fact, in all 30 cases, the serum folic acid level was well below the minimum normal level.[7]

In order to determine whether folic acid supplementation has a beneficial effect on patient's anemia, this study was conducted on thalassemic patients in Bou-Ali Sina Hospital in May 2004.

Patients and Methods

This study was a randomized placebo-controlled clinical trial. The patients enrolled in this study had thalassemia major on regular blood

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transfusion. None was pregnant/lactating, had chronic liver disease, used folic acid supplements or medicines affecting folic acid metabolism. After explaining the project, a written informed consent form was signed by each patient or their parent/guardian. The sample size was calculated as 20 in each group by the following assumptions: a power of 90%, confidence level of 95%, standard deviation of hemoglobin (Hb) level = 1 g/dL and anticipated effect of folic acid on Hb of 1 g/dL. The socioeconomic status of patients was determined through questions regarding their formal educational level, job, ownership of residential place, and the type of their medical insurance. A blood sample was then taken and serum folic acid measured by the radioimmuno-assay (RIA) method, using the standard method[8] (Delshid gamma counter, Iran). Kits were obtained from the ICN Pharmaceutical (USA). Normal serum levels determined by the kit were in the range of 1.5 – 16.9 ng/mL with a sensitivity of 0.6 ng. Patients were then ranked according to their serum folic acid and each pair of patients with the same folic acid level was randomly assigned (head/tail) to take either placebo (controls) or folic acid (cases). Placebo tablets made by Faculty of Pharmacy, Mazandaran University of Medical Sciences, had the same size and color as the test drug—folic acid tablets (1 mg tablets, obtained from Iran Daru Pharmaceutical Company, Iran). The patients were asked to take one tablet per day and return for blood test four weeks later while continuing their treatment routines, as usual. The mean values of hemoglobin, hematocrit, red cell count, MCV, MCH, MCHC, and blood transfusion intervals during a period of three months, before and after the intervention, were recorded.

Data were analyzed using SPSS-10 statistical software, through the *Student's t*-test between groups and the paired *t*-test within the groups.

Results

Fifty-one participants (23 controls and 28 cases) were studied with a drop-out of 5 patients in control group. The control group, consisting of 12 (43%) females and 16 (57%) males, had a mean ± SD age of 16.8 ± 6 years. The study cases, comprised 8 (28.5%) females and 20 (71.5%) males, had a mean ± SD age of 17 ± 5 years. The socioeconomic status of the patients was poor in 40% of control and 48% of case groups. The mean ± SD serum folic acid level was severely low—0.8 ± 0.6 ng/mL—in 15 (29%) patients before the trial. Considering the minimum accepted level,[2] 68% of patients had folic acid deficiency (serum level <3 ng/mL).

Table 1 shows the details of complete blood count measured in the two groups. The mean level of folic acid was increased significantly ($P < 0.0001$) after the intervention in case group (Table 1). Nonetheless, the transfusion interval, hemoglobin level, and red cell indices were not changed.

After treatment with placebo, the blood transfusion interval in the control group became significantly ($P < 0.03$) longer (Table 1).

There were several patients in both groups with severe folic acid deficiency eight belonging to the control group (mean ± SD serum folic acid level of 0.8 ± 0.7 ng/mL) and seven to the case group (mean ± SD serum folic acid level of 0.7 ± 0.5 ng/mL). After folic acid supplementation, these levels were found to be 1.5 ± 2 ng/mL in the control and 8.8 ± 1.9 in the case groups ($P < 0.0001$). However, in this subgroup again, complete blood count and transfusion intervals were not changed significantly. No side effects were reported.

Discussion

We found that folic acid deficiency was present

Table 1. The effect of administration of folic acid on hematological profile of patients with β-thalassemia major. Figures are mean ± SD.

Parameter	Control (n = 23)		*P* value	Case (n = 28)		*P* value
	Before	After		Before	After	
RBC($\times 10^6/\mu L$)	3.47 ± 0.44	3.57 ± 0.4	<0.3	3.45 ± 0.51	3.53 ± 0.5	<0.6
Hb (g/dL)	9.06 ± 1.01	9.41 ± 1.18	<0.1	8.85 ± 1.27	9.26 ± 1.78	<1
Hct (%)	27.5 ± 3.7	28 ± 3.3	<0.1	27.6 ± 2.7	28.5 ± 5.1	<0.4
MCV (fL)	77.7 ± 3.4	76.3 ± 10.7	<0.4	76.3 ± 3.9	76.7 ± 3.8	<0.9
MCH (pg)	26.1 ± 1.3	26.4 ± 1.5	<0.3	25.8 ± 1.6	26.1 ± 1.7	<0.6
MCHC (%)	33.5 ± 1.3	33.7 ± 1.4	<0.5	33.8 ± 0.8	34 ± 1.5	<0.6
Transfusion interval (day)	20 ± 5.5	23 ± 8.4	<0.03	20.2 ± 5.2	20.4 ± 5.3	<0.8
Serum folic acid (ng/mL)	4 ± 4.5	3.1 ± 2.8	<0.3	3.4 ± 2.5	9 ± 3.6	<0.0001

RBC = red blood cell (count); Hb = hemoglobin; Hct = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

in 29 – 68% of subjects, depending on how we define the deficiency threshold.

Although folate deficient, these patients had still low mean corpuscular volume (MCV). Therefore, MCV is not a good predictor for the presence of the concomitant folic acid deficiency. Consequently, either serum folic acid should be measured periodically or preventive supplementation of folic acid should be administered routinely to undertransfused thalassemic patients. The latter condition is unfortunately the case in the most developing countries where there is a large number of patients and limited supply of donated blood.

Even in this group of patients, correction of folic acid deficiency had no benefit in terms of the anemia and blood requirements. Therefore, administration of large amounts of folic acid to improve patient's anemia is not recommended. This practice is done by some physicians, who take care of thalassemic patients.

Prolongation of transfusion interval in controls is not significant clinically and it may be due to coincidence factors like holidays in follow-up period.

Encountering folic acid deficiency was rather a surprise in our first study,[7] because diet of people in the region is full of fresh vegetables and they usually drink plenty of tea. In spite of undertransfusion, these patients received red cells donated by people who are not folic acid deficient. This shows that patients with thalassemia major are really in need of extra folic acid to fulfill their requirements.

Regarding the role of homocystein (Hcy) as a risk factor for arteriosclerosis, Harker et al in 1976 published a paper; thereafter, other studies confirmed his findings.[9] A meta-analysis of 27 researches showed that the risk for developing coronary disease in patients with a high serum Hcy is up to 3.2 times of those with normal serum Hcy; the risk for development of cerebral and peripheral vessel disease is between 1.6 and 6.8.[10]

Folic acid supplementation for uremic patients under chronic dialysis has been explored by other scientists.[9] McGregor et al showed that administration of 5 mg/day folic acid to uremic patients could decrease their blood Hcy level.[9]

We showed that administration of 1 mg/day of folic acid for one month could correct its deficiency. As the follow-up period was short, effects on growth or susceptibility to infections were not investigated.

In conclusion, we recommend prophylactic and routine folic acid supplementation for all patients with β-thalassemia major and intermedia.

References

1 Behrman RE, Kliegman RM, Jensen HB. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004: 163.

2 Lee GR. *Wintrobs Clinical Hematology: Megaloblastic and Nonmegaloblastic Microcytic Anemias*. 9th ed. Philadelphia: Lee and Febiger; 1993: 773.

3 Vatanavicharn S, Anuvatanakulchai M, Na-Nakorn S, Wasi P. Serum and erythrocyte folate levels in thalassaemic patients in Thailand. *Scand J Haematol*. 1979; **22:** 241 – 245.

4 Castagna PC, Fedeli F, Fusco AM, Montani L, Radaelli F, Tartara R. Behavior of blood folate in children with thalassemia major under transfusion therapy and in thalassemia trait. *Acta Vitaminol Enzymol*. 1984; **6:** 183 – 188.

5 Danel P, Girot R, Tchernia G. Thalassemia major manifested by megaloblastic anemia caused by folate deficiency. *Arch Pediatr*. 1983; **40:** 799 – 801.

6 Eleftherio A. *About Thalassemia*. Cyprus: Thalassemia International Federation Publication; 2003.

7 Kosaryan M, Mahdavi MR, Shahmoradi M, Arabzadeh M, Maleki I. Is it necessary to give folic acid to thalassemia minor or major? International Congress on Pediatrics. Tehran, Iran; 2003.

8 Sullivan LW. Megaloblastic anemias. In: Mengel CE, Frei E, Nakhman R, eds. *Hematology; Principles and Practice*. Chicago: Yearbook Medical Publishers; 1972: 95 – 131.

9 McGregor D, Shand B, Lynn K. A controlled trial of the effect of folate supplements on homocysteine, lipid, and hemorheology in end-stage renal disease. *Nephron*. 2000; **85:** 215 – 220.

10 Hankey GY, Eikelboom JW. Homocystein and vascular disease. *Lancet*. 1999; **354:** 407 – 413.