Original Article

Iran J Ped Hematol Oncol. 2017, Vol 7.No 3, 232-236

The Efficacy of Vitamin E and Folic acid on the Acute Hemolysis Caused by Glucose-6 phosphate Dehydrogenase

Bahram Darbandi MD[1], Sharareh Zarezadeh MD[1], Zahra Atrkar Roshan PhD[2], Afagh Hassanzadeh Rad MSc[1], Adel Baghersalimi MD[1,*]

1. Pediatrics Growth Disorders Research center , 17 shahrivar Pediatric Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
2. School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
*Corresponding author: Dr. Adel Baghersalimi, Pediatrics Growth Disorders Research center , 17 shahrivar Pediatric Hospital, Siadati Street, Rasht, Iran. Email: Baghersalimi498@yahoo.com.

Received: 22 September 2016 **Accepted:** 12 April 2017

Abstract

Background: Glucose-6 phosphate dehydrogenase (G6PD) deficiency is the most common inherited enzyme deficiency of red blood cells involving the enzyme pathway of hexose monophosphate. This study was conducted to examine the effect of vitamin E and folic acid on the improvement of acute hemolysis caused by the G6PD deficiency in patients referred to 17 Shahrivar Hospital, Rasht.

Materials and Methods: This was a randomized clinical trial conducted on 120 patients with G6PD deficiency. The patients were divided in 4 groups, including vitamin E, folic acid, a combination of both supplements, and control groups. The hemoglobin level and the reticulocyte count of patients during hospitalization, at discharge and two weeks after discharge were evaluated. All patients received standard treatment for acute hemolysis.

Results: Mean age of the patients was 44.19± 16.43 months. There was no significant difference between 4 groups in terms of age, gender, and etiology of hemolysis ($p>0.05$). The consumption of fava bean was the main cause of hemolysis in 95% of patients. The level of hemoglobin and hematocrit, and reticulocyte count during hospitalization and discharge among groups showed no significant difference ($p>0.05$). However, a significant increase was observed in the level of hemoglobin and hematocrit and reduction of reticulocyte count in patients receiving supplements compared with control group ($p=0.001$).

Conclusion: Considering the low cost, availability, and safety profile of theses supplements, it seems that usage of folic acid and vitamin E can be highly recommended during favism.

Key words: Favism, Folic Acid, Vitamin E, Hemolysis, Glucose-6 phosphate dehydrogenase

Introduction

Glucose-6 phosphate dehydrogenase (G6PD) deficiency is the most common inherited enzyme deficiency of red blood cells involving the enzyme pathway of hexose monophosphate (1, 2). Although about 500 million people worldwide suffer from this enzyme deficiency, most of affected individuals are asymptomatic (3). Clinical states related to G6PD deficiency are neonatal jaundice, chronic non spherocytic hemolytic anemia or acute hemolysis attack following the damage of oxidant caused by the consumption of some drugs and fava bean or facing with chemical materials like naphtaline. Acute hemolysis attack is self-limited in most instances and its treatment is supportive. Intravenous fluids are given with or without bicarbonate to prevent the renal damage caused by the sediment of hemoglobin (5, 6) and in some cases; blood transfusion might be needed (5-7). In the most severe type of this disorder that causes chronic hemolysis, therapeutic measurements include splenectomy, blood transfusion, folic acid, and antioxidants such as vitamin E(8). In some parts of Iran, including Guilan province on the coast of Caspian sea, the most severe Mediterranean form (class II according to World Health Organization (WHO) classification) is common and causes the incidence of hemolysis attack following the consumption of fava bean (favism)(9).

The incidence of G6PD deficiency in Guilan province is reported as 6.4 % (10).
In spite of the known role of folic acid and vitamin E in patients with chronic hemolysis caused by the G6PD deficiency, there is little information about the effectiveness of these two supplements during acute hemolysis caused by this enzyme deficiency (11 - 14).
This study was conducted with the aim of comparing the effectiveness of vitamin E and folic acid and combination of these two supplements on enhancement of acute hemolysis caused by the G6PD deficiency in children.

Materials and Methods

This clinical trial was conducted from June 2014 to June 2015 in 17 Shahrivar Pediatric Hospital, Rasht, on children with G6PD deficiency induced acute hemolytic anemia. The ethical approval was obtained from the Ethics Committee of Guilan University of Medical Sciences (1930309902, 2014-09-16) and the IRCT code was also obtained (IRCT2014102019541N1).
Inclusion criteria of the current investigation were 1-14 years of age, suffering from the G6PD deficiency, hospitalization due to acute hemolysis, and lack of using vitamin E and folic acid with therapeutic dose during the last month. Exclusion criteria were lack of follow up for testing, the death of patient before the end of the study, and acute hemolysis induced by other causes than G6PD deficiency.
Observing the exclusion and inclusion criteria, 120 patients were recruited and then were randomly divided into 4 groups. Group 1 was taken vitamin E daily (1 to 2 years: 100 mg per day, 2 to 3 years: 200 mg per day, 3 to 4 years: 300 mg per day and above 4 years: 400 mg). Group 2 was taken folic acid daily (1-2 years: 2mg and, for age group above 2 years: 5mg). Group 3 consumed a combination of both supplements daily. These 3 groups received supplements for 2 weeks after discharging. However, group 4 was given no supplement and they were considered as control group.
The levels of hemoglobin, hematocrit, and the reticulocyte count of the patients were evaluated during hospitalization, at discharge and two weeks after discharging using SYSMEX cell counter. All patients received standard treatment for acute hemolysis induced by G6PD deficiency, including intravenous fluid therapy. If the patient needed blood transfusion, the volume of blood and frequency of transfusion were recorded separately on a checklist. Informed consent was obtained from parents of all patients before enrollment. in addition, all the participants had this right to leave the study at any time.

Statistical analysis

After completing checklists, data were analyzed using SPSS (version 21).The results for quantitative variables were expressed as mean and standard deviation (mean± SD) and the results for qualitative variables were expressed as absolute and relative frequency. T-test and ANOVA were used to compare the quantitative variables among groups and chi-square test was used to compare qualitative variables. P.value <0.05 was considered as significant level and 95% confidence interval was noted.

Results

The mean age of patients was 44.19± 16.43 with a minimum age of 14 and maximum age of 108 months. With respect to gender, 64.2 % (77 patients) were male and 35.8% (43 patients) were female. There was no statistically significant difference among 4 groups according to age, gender, and etiology (p>0.05). Consuming fava bean was the reason of the incidence of hemolysis in 95% of the patients. The level of hemoglobin, hematocrit, and reticulocyte count showed no statistically significant difference among groups during hospitalization and at the discharge.(p>0.05)

However, the increase of hemoglobin level and hematocrit and reduction of reticulocyte count were observed two weeks after discharging in the first three groups in comparison with the control group (p=0.001). The mentioned indices between the first three groups showed no statistically significant difference two weeks following discharge. Table I shows demographic characteristics and hematologic parameters of patients across 4 groups.

Table I: Demographic characteristics and hematologic parameters of patients

	Control (group 4)	**Folic acid + Vitamin E (group 3)**	**Folic Acid (group 2)**	**Vitamin E (group 1)**	
Sex(%)					Total
Male	18(60)	19(63.7)	19(63.7)	21(70)	77(64.2)
Female	12(40)	11(37.3)	11(37.3)	9(30)	43(35.8)
Mean of age (month)	43.73	44.63	47.33	36.93	Total: 43.16
Fava as etiology of hemolysis	30(100%)	28(93.4%)	26(86.6%)	30(100%)	Total: 95%
Mean Hb g/dl (±SD)					
On admission	6.68(±1.60)	6.62(±1.56)	6.61(±1.34)	6.93(±1.41)	P*=0.819
On discharge	10.82(±1.50)	10.11(±1.10)	10.49(±1.24)	10.03(±1.19)	P*=0.065
2 week later	10.77(±1.40)	13.35(±0.88)	13.03(1.02)	12.2(1.01)	P*=0.001
Mean Retic. % (±SD)					
On admission	2.76(±1.40)	3.03(±1.17)	3.37(±1.62)	3.41(±1.56)	P*=0.262
On discharge	1.68(±0.63)	1.63(±0.44)	1.66(±0.46)	1.56(±0.35)	P*=0.782
2 week later	1.32(±0.59)	0.92(±0.15)	0.92(±0.19)	0.91(±0.23)	P*=0.001

*ANOVA and T-test were used, P. value considered significant if < 0.05

Disscussion.

To the best of our knowledge, the current research was one of the rare, if any, clinical trial revealing the effectiveness of folic acid and vitamin E on improvement of blood indices in acute hemolysis caused by the G6PD deficiency. As fava bean led to hemolysis in 95% of our patients, it seems that these two supplements can play an important role in treatment of favism. The results of the present study indicated that administering short-term folic acid or vitamin E alone or together can increase the level of hemoglobin and hematocrit significantly and reduce the level of reticulocyte count. Concurrent use of folic acid and vitamin E was more effective than taking each of them separately, although it was not statistically significant. The role of folic acid in the treatment of different types of hemolytic anemia such as hereditary spherocytosis and thalassemia has already been proven (15, 16). The severe need of bone marrow cells to folates is the most important reason for increasing need to this supplement (17). In the current research, results showed that folic acid consumption can improve hematologic parameters in favism strongly.

Administering vitamin E in some types of hemolytic anemia such as sickle cell anemia and different kinds of thalassemia syndromes can reduce the severity of hemolysis(8). Corash et al., and sultana et al., separately revealed that administering vitamin E is effective in improving the life span of red blood cells and in reducing hemolysis (especially chronic hemolysis) in the G6PD deficiency (12, 13). The current study demonstrated that shorter use of vitamin E with similar doses is effective on favism. Although the rate of its effectiveness was less than two other groups but it was not statistically significant.

Considering the different mechanism of effectiveness of these two supplements during hemolysis, it seems that the concurrent use of folic acid and vitamin E had higher efficacy in comparison with the consumption of each alone.

Conclusion

Short term use of folic acid and vitamin E or a combination of these two in acute hemolysis caused by the G6PD deficiency improved significantly the trend in increasing the hemoglobin and hematocrit. However, concurrent use of these two supplements increased blood indices more effectively. Considering the low cost, availability, and safety profile of theses supplements, of the consumption of folic acid and vitamin E is highly recommended during favism. Further studies are needed to assess the effect of early usage of these supplements on blood transfusion.

Acknowledgement

This investigation was based on the thesis submitted by the second author (sharareh zarezadeh) to the Guilan University of Medical Sciences. This study was done with financial support provided by vice chancellor of research in Guilan University of Medical Sciences.

Conflict of interest

Authors declare that authors have no conflict of interest.

References

1. Segel GB, Hackeny LR. G1ucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies. In: Behrman RE, KliegmanRM, Stanton BF, Schor NF and et al . Nelson Textbook of PEDIATRICS.20th Edition. Philadelphia: ELSEVIE SAUNDERS Inc,2016:2355-2357

2. Darbandi B, Noghbaei M, Mehrabian F, Jafroodi M. Medical expenses of patients with Favism admitted to 17th Shahrivar Hospital compared to G6PD enzyme screening cost, in north of Iran. IJPHO 2014; l4(2):53-56.

3. Luzzatto L, Poggi V. Glucose-6-Phasphate Dehydrogenase Deficiency. In : Orkin SH, Nathan DG, Ginsburg D and et al. Hematology and Oncology of Infancy and Childhood. 8thEdition.Philadelphia: Elsevier Inc; 2015:609-629.

4. Lanzkowsky P. Manual of PediatricHematology and Oncology. 5th ed. London: Elsevier; 2011: 196-7

5. Monga A, Makkar RP, Arora A, Mukhopadhyay S, Gupta AK.Case report: Acute hepatitis E infection with coexistent glucose-6-phosphate dehydrogenase deficiency. Can J Infect Dis 2003;14 (4): 230–1

6. Hamilton JW, Jones FG, McMullin MF.Glucose-6-phosphate dehydrogenase Guadalajara – a case of chronic non-spherocytic haemolytic anaemia responding to splenectomy and the role of splenectomy in this disorder. Hematology 2004; 9 (4): 307–9.

7. Cappellini MD, Fiorelli G .Glucose-6-phosphate dehydrogenase deficiency. Lancet2008; 371 (9606): 64–74.

8. Jilani T, Iqbal MP. Does vitamin E have a role in treatment and prevention of anemia? Pak. J. Pharm. Sci 2011; 24(2): 237-242.

9. Farhud DD ,Yazdanpanah L. Glucose-6-phosphate dehydrogenase (G6PD) Deficiency. IJPH 2008; 37(4): 1-18.
10. Khalili D, Jafroodi M, Sajedi S. Survey of the prevalence of Glucose-6-Phasphate Dehydrogenase deficiency in Rasht, Iran. J Gui Univ Med Sci 2007; 16 (63): 51-56.
11. Eldamhougy S, Elhelw Z, Yamamah G.The vitamin E status among glucose-6 phosphate dehydrogenase deficient patients and effectiveness of oral vitamin E. Int J Vitam Nutr Res 1988;58(2):184-8.
12. Corash L, Spielberg S, Bartsocas C, Boxer L. Reduced chronic hemolysis during high-dose vitamin E administration in Mediterranean-type glucose-6-phosphate dehydrogenase deficiency. NEJM1980 ; 303(8):416-20 .
13. Sultana N, Begum N, Akhter S, Begum S. Role of vitamin E supplementation on serum levels of copper and zinc in hemolytic anemic patients with G6PD deficiency. Mymensingh Med J 2008;17(2):S84-90.
14. Hafez M, Amar ES, Zedan M. Improved erythrocyte survival with combined vitamin E and selenium therapy in children with glucose-6-phosphate dehydrogenase deficiency and mild chronic hemolysis. J Pediatr 1986;108(4):558-61.
15. Mojtahedzadeh F, Kosaryan M, Mahdavi M. The effect of folic acid supplementation in beta thalassemia major: A randomized placebo controlled clinical trial. Arch Iran Med 2006 9 (3): 266 – 268.
16. Bolton-Maggs PH, Stevens RF, Dodd NJ. Guidelines for the diagnosis and management of hereditary spherocytosis. Br J Hae¬matol 2004;126(4):455–474.
17. Sankaran VG, Nathan DG, Orkin SH. Thalassemias. Orkin SH, Nathan DG, Ginsburg D and et al. Hematology and Oncology of Infancy and Childhood. 8thEdition.Philadelphia: Elsevier Inc; 2015:715-769.