Original Article

Iran J Ped Hematol Oncol. 2016, Vol6.No3,157-165

Effect of Sodium Bicarbonate and Sodium Chloride on Renal and Hematologic Factors in Patients with Glucose-6-phosphate Dehydrogenase Deficiency

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Received: 9 March 2016 **Accepted:** 28 July 2016

Abstract

Background: Sodium bicarbonate serum therapy is used for compensation bicarbonate lost and increasing blood pH in metabolic acidosis caused by severe anemia in patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The aim of present study was comparison the effect of serum therapy using two different serums (serum with bicarbonate and without bicarbonate) on some renal and hematologic factors and their side effects in patients with hemolysis caused by G6PD deficiency.

Materials and Methods: In this clinical trial study, 79 patients with favism randomly put into two treatment groups, sodium bicarbonate and sodium chloride fluid therapy. During treatment, patients received blood based on hemoglobin (Hb). Duration of hospitalization, times of Blood transfusion, received blood volume, duration of cleaning UA of Hb, Hb, urine pH and granular casts in UA were evaluated.

Results: The mean age of patients was 51.22 ± 37.86 months and there were 58 males and 21 females. Only duration of hospitalization and urine pH statistically showed a significant difference between two treatment groups (P=0.036 and P> 0.01, respectively), and other factors were statistically almost identical.

Conclusion: The efficiency of sodium chloride was more than sodium bicarbonate in reducing the duration of hospitalization and the small clinical difference between received blood volumes, hemoglobin changes and duration of removing hemoglobin in UA, suggest, properly, sodium chloride can be more effective on improvement of hemolysis. Lack of side effects such as metabolic acidosis, heart damage and kidney failure in children can be due to controlled injection method, the concentration of soluble drugs and small size of studied population.

Keywords: G6PD, Favism, Hemolysis, Hemolytic Anemia, Sodium Bicarbonate

Introduction

Golucose-6-phosphate dehydrogenase (G6PD) deficiency is a heredity genetic deficiency linked to X chromosome that occurs due to mutation in G6PD gene. It causes protein variety with different levels of enzyme activity that leads to a wide range of clinical and biochemistry phenotype (1). G6PD is a key enzyme to keep the reduction potential and act by producing NADPH (Nicotinamide adenine

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dinucleotide phosphate) in pentose phosphate pathway. Generally, the most common clinical manifestations due to G6PD deficiency are as followings; neonatal jaundice, favism, acute hemolytic anemia and chronic hemolytic anemia (1, 2).

Consumption of oxidative drugs and medicinal plants such as Primaquine, Hanna, tea and polyphenols, eating beans in patients with favism as well as bacterial, viral and rickettsia infections especially in hepatitis, pneumonia and typhoid fever leads to acute hemolytic anemia. People with chronic hemolytic anemia have low enzyme activity and suffer from hemolytic anemia even in the absence of oxidative agents. This abnormality is usually observed during childhood (2-7).

Studies show that more than 400 million people in the world have G6PD enzyme deficiency (8). Most of G6PD deficiencies have been reported in Africa, Southern Europe, Middle East, Southeast Asia and Central and South Pacific Islands. However, they have been spread due to the recent immigration of defective alleles in North and South America as well as parts of northern Europe (8). Several studies have mentioned 62% prevalence in the Middle East (especially the Kurds) and 31% in North Vietnam (9, 10). According to the World Health Organization (WHO), Iran is located in an area which the prevalence of G6PD deficiency is moderate to high (11). In general the incidence of this defect is 9.14-10% in Iran. The higher prevalence was observed in the northern and southern provinces of Iran. So that the incidence in the northern, southern and the southeast provinces of Iran was reported 8.6-16.4%, 12% and 19.3% respectively (12-15).

Tissue hypoxia may be caused due to severe anemia and metabolic acidosis occurs as a result. Acidosis is a process that leads to an abnormal increase in the concentration of hydrogen ions and results in reduction of blood pH to below 7.3. Concentration of bicarbonate as well as CO2 pressure maybe decreased or remains normal. In these circumstances, sodium bicarbonate is one of medicines that are used to compensate the lost bicarbonate and increasing pH (16, 18). This effect of sodium bicarbonate has been confirmed in some previous studies (19, 20, 21); however others reject that because of some disadvantages (18, 22). Fluid and sodium load are the main side effects of bicarbonate intake. This can cause abnormal rise in blood plasma, osmolar concentration, blood sodium as well as reduction in arterial pressure and temporary increased intracranial pressure that maybe associated with hypertonic property (22). Avoiding oxidative stress (such as drugs and Bean) is the main treatment to control this disease. In cases of severe hemolysis, blood transfusion is done. Maintaining hydration and urine alkalization prevent kidney damage caused by free hemoglobin sediment (23). In general, blood transfusion in children with acute hemolytic anemia is done according to a guideline which includes: 1) If the amount of hemoglobin is below 7 g/dl, transfusion should be done 2) If the amount of hemoglobin is above 9 g/dl, or if the hemoglobin level is between 7 and 9 g/dl and there is no persistent hemoglobinuria, the patient should be monitored for at least 48 hours. During this time if conditions 1 or 2 occures transfusion should be done (24).

In neonatal jaundice due to G6PD deficiency, similar to neonatal jaundice of other reasons, treatment of high concentrations of bilirubin is controversial. When the concentration of unconjugated bilirubin reaches to 150 μmol/L, phototherapy will be done to prevent damage to the nervous system (9). Patients with non-spherocytic hemolytic anemia sometimes have compensable anemia and does not require blood transfusion, but these people should be monitored for each stimulant (such as an infection or an oxidative agent) causing severe anemia in them (9). Congenital non-spherocytic

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hemolytic anemia is rarely associated with injection so there is little need to iron chelation therapy (9). The project objective was to compare the effect of two fluid therapy methods (serum bicarbonate and serum without bicarbonate) on some renal and hematologic factors and their side effects in patients with hemolysis caused by enzyme glucose-6-phosphate dehydrogenase deficiency referred to Taleghani hospital, Gorgan, Iran.

Materials and Methods

Patients

This was a randomized clinical trial study and has been recorded in clinical trial designs site (IRCT) with code number IRCT2013031012765N1. Seventy nine favism patients with the age range of 11-180 months referred to Taleghani hospital, Gorgan, Iran during March,2013- Jun, 2015 were studied in this project. Favism was the only inclusion criteria in these patients. Inclusion in the study was voluntary and all the information will be treated confidentially and patients will be identified by a code. Consent form was completed by parents of patients. History of bean consumption and dark urine are early evidence of favism diagnosis. Favism was confirmed through positive hemoglobinuria urinalysis. An exclusion criterion was lack of patient satisfaction. At the beginning of the test, clinical and laboratory parameters were evaluated. Clinical factors included time from admission to discharge, number of transfusions, received blood volume and paraclinical factors included hemoglobin, urinary pH, the time of clearing UA from hemoglobin and the granular casts.

Sample collection and processing

3 ml blood sample and 10 ml of urine sample were collected from patients. Patients were randomly assigned to the study so that one referred patient treated with serum containing sodium bicarbonate and sodium chloride was used for next one in determined period of time. 5% dextrose water was used 1.5 times of the maintenance serum for one patient and per 100 ml serum, 3 mEq of NaCl was added. And for the next patient the same serum volume of 5% dextrose water was used and per 100 ml serum, 3 mEq of sodium bicarbonate was added. Then patients were divided into three groups. The first group, packed cell was asked for whom with hemoglobin less than 7. The second group A, if the hemoglobin was between 9-7 g/dl and there was hemoglobinuria urine, packed cell was injected under the previous protocol. The second group B, in the absence of hemoglobinuria, the patient was hospitalized and monitored for 24 hours and if during this period first or second conditions were created specified actions were done according to the protocol. The third group, hemoglobin was higher than 9 g/dl and there was hemoglobinuria so patients were hospitalized and monitored for 24 hours and if during this period first or second conditions were created specified actions were done according to the protocol and if with this amount of hemoglobin, there was no hemoglobinuria, patients were excluded from the study. At discharge time, clinical and paraclinical factors were evaluated again. For this purpose, again 3 ml of blood and 10 ml urine samples were taken from patients. A checklist was completed for each patient and all information related to the clinical and paraclinical factors as well as their personal profile were recorded.

Statistical analysis

SPSS version 16 was used in order to analyze the data. Kolmogorov-Smirnov test was used to assess the normality of the data. Also nonparametric statistical tests such as Kruskal-Wallis test, t-test, Wilcoxon and analysis of covariance were used.

Results

A total of 79 patients with hemolysis caused by a deficiency of the enzyme glucose-6-phosphate dehydrogenase with

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favism presentation were assessed in this clinical trial study. Patients were 58 (73.4%) males and 21 (26.60 %) females with the average age of 51.22 ± 37.86 months. They were randomly divided into two groups, including treated with serum containing sodium bicarbonate (n=43) and treatment with serum containing sodium chloride (n= 36) (Figure 1). Baseline demographic Characteristics of 79 patients in both groups has been shown in Table I.Clinical and paraclinical factors were examined in both fluid therapy methods which are shown in Tables II and III.

Reviewing the normality of data using the Kolmogorov-Smirnov test revealed that blood volume and the number of blood transfusions were not normal. So the Kruskal-Wallis nonparametric test was used for data analysis between two groups in points of blood volume and the number of blood transfusions. Based on this test, there was no significant difference (P> 0.05) (Table III). Duration of hospitalization till discharge as well as duration of negative UA in terms of hemoglobin were normal and were analyzed using t-test analysis. According to the test, duration of hospitalization between two groups showed significant difference (P= 0.036), but duration of negative UA in terms of hemoglobin was not significant (P> 0.05) (Table III).

In reviewing the amount of hemoglobin given the normal distribution of hemoglobin before and after treatment in both groups, the equality of hemoglobin level in both groups before treatment was examined based on T-distribution and then the final analysis was performed using covariance method. The results suggested that there was no significant difference between two groups (P> 0.05). Reviewing urine pH before and after treatment in both groups Wilcoxon test was used for analysis due to lack of normal distribution of data which showed a significant difference between two groups (P< 0.01). No specific side effects were observed in patients of both groups. Also no granular casts were found in the urine samples of the patients.

Table I: Baseline demographic characteristics of patients with G6PD deficiency based on baseline hemoglobin in both therapeutic strategies

Characteristics		Sodium bicarbonate (n=43)	Sodium chloride (n=36)
Mal, No. (%)		33 (77)	25 (70)
Female, No. (%)		10 (23)	11 (30)
Age, mean (SD*) [range], m		47.19 (37.84)[11-156]	56.65 (38.27)[12-180]
Weight, mean (SD) [range], kg		17.80 (8.05) [10-48]	16.74 (7.80) [10-53]
Hemoglobin (mg/ml)	<7, No. (%)	29 (36.71)	29 (36.71)
	7-9, No. (%)	7 (8.86)	13 (16.45)
	9<, No. (%)	0.0	1 (1.26)

* Standard deviation

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Table II: Clinical and Paraclinical factors in patients with G6PD deficiency in both therapeutic strategies

	Mean (SD)*	
	Sodium bicarbonate	Sodium chloride
Hemoglobin before treatment (mg/ml)	5.96 (1.80)	5.90 (1.62)
Hemoglobin after treatment (mg/ml)	9.65 (1.26)	10.09 (1.46)
urine pH before treatment	6.28 (0.9)	6.18 (1.07)
urine pH after treatment	7.65 (0.92)	6.88 (0.73)
Time of clarify UA In terms of hemoglobin	36.37 (17.86)	31.39 (18.61)
Duration of admission till discharge (Hour)	45.81 (17.58)	37.30 (17.80)
Number of blood transfusions	1.60 (0.63)	1.47 (0.7)
Received blood volume (ml)	171.63 (62.26)	164.43 (74.78)

* Standard deviation

Table III: Comparison of clinical and paraclinical factors in patients with G6PD deficiency in both therapeutic strategies

Factor			*P-value*
Hemoglobin changes	Between groups		*0.351*
	Within group	Sodium bicarbonate	*<0.001*
		Sodium chloride	*<0.001*
Changes in urinary pH	Between groups		*0.001*
		Sodium bicarbonate	*<0.001*
		Sodium chloride	*0.002*
Duration of admission until discharge			*0.036*
Number of blood transfusions			*0.223*
UA negative duration In terms of hemoglobin			*0.230*
Received blood volume			*0.416*

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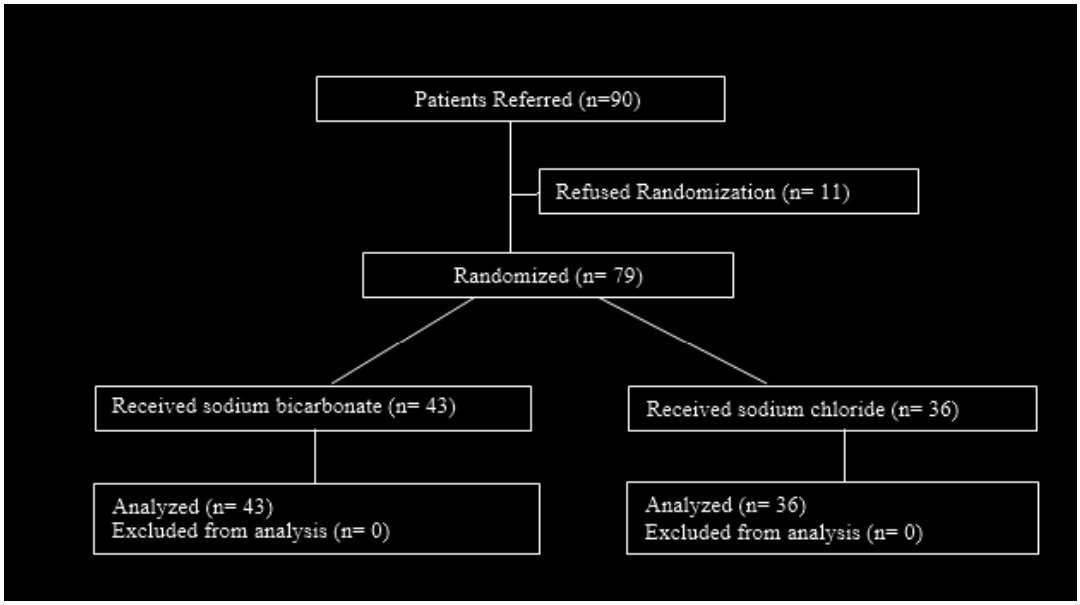

Figure 1. Study flow and distribution of procedures

Discussion

One of the causes of hemolysis is hereditary disorders such as enzymes disorders that the most common one is G6PD deficiency. Hemoglobin reduction and the intravenous hemolysis occur in this disorder (25). Reduction of glutathione in patients with G6PD deficiency results in hemolysis (26).There is no special treatment and in extreme cases, blood transfusions should be done. Generally, increase of indirect bilirubin and lactate dehydrogenase, as well as reduction of the amount of haptoglobin cause by lysis of red blood cells. Thus, lactate dehydrogenase and hemoglobin are released into the bloodstream (25). Metabolic acidosis occurs as a result of hemolysis and severe anemia in which organic acids such as lactic acid increase in the blood. Sodium bicarbonate is used in order to resolve this condition (18). Present study is one of the few studies which have compared the effects of two types of serum containing sodium bicarbonate and without bicarbonate (sodium chloride) in patients with G6PD deficiency presenting favism and cheched out the side effects of serum bicarbonate in these patients. Factors such as hemoglobin level, urine pH, the urine color in terms of negative hemoglobin, received blood volume, number of blood transfusions and duration of hospitalization have been examined in this study. It was observed that among the aforementioned factors only time from admission to discharge (duration of hospitalization) ($P = 0.036$) and changes in urinary pH ($P < 0.01$) showed a significant difference between the two theraputic methods among patients. The results showed that the mean duration of hospitalization in sodium bicarbonate group and sodium chloride group were 45.18 ± 17.58 and 37.30 ± 17.80, respectively. Although Szeto et al., (2003) in a study on the effect of oral sodium bicarbonate in treatment of metabolic acidosis in peritoneal dialysis patients showed that the duration of hospitalization was shorter in comparison with the group receiving placebo (19). But, the present study revealed that sodium chloride is effective in reducing the duration of hospitalization. Received blood volume and duration of clarification of urine in terms of hemoglobin although

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statistically didn't show significant difference between the two groups, but in detailed clinically review are different and in sodium chloride group have lower values than sodium bicarbonate group. So, these factors can affect the length of hospitalization. The patient may develop cyanosis, headache, fatigue, palpitations, shortness of breath, lethargy, pain in the back and sternum, abdominal pain, splenomegaly, hemoglobinuria as well as icteric sclera. Also the compounds resulting from the degradation of hemoglobin accumulate in the blood and lead to jaundice or excrete via urine and cause a dark brown appearance of urine (27). In general, in metabolic acidosis condition urinary pH decreases due to an increase in the ability of the kidneys in excretion of acidic hydrogen ions of the blood (18). On the other hand, one of the major complications of severe hemolysis is kidneys disruption. In such condition, using fluids and alkaline diuresis increase pH to above 6.5 (28). The results of this study showed that sodium bicarbonate increases urinary pH more than sodium chloride. Sodium bicarbonate directs intracellular water flow into the extracellular space and thus leads to return of the osmotic balance as well as raising hemoglobin (29). When the healthy volunteers developed acidification complications using acetazolamide and then were treated with sodium bicarbonate, it was observed that an increase of hemoglobin affinity for oxygen occurred due to pH correction (9). In blood acidification, oxygen delivery is impaired by hemoglobin. The duration of this reaction is about 8 hours which is thought to be due to the Bohr Effect as well as delayed effect of 2, 3-phosphoglycerate on hemoglobin-oxygen affinity (22). Thus it was seen that there is a direct relationship between increased hemoglobin, blood pH correction and urinary pH so in both groups hemoglobin and urinary pH changes was significant (P< 0.001). The results of this study didn't show any statistically significant difference (P> 0.05) in hemoglobin changes in both groups after treatment. But clinically in sodium chloride group, hemoglobin had a greater increase (about 0.44) and indicated that there is a linear relationship between the increase of hemoglobin and pH.

Merten et al., (2004) performed a controlled randomized clinical trial on the effect of sodium bicarbonate in preventing contrast nephropathy in the radiography. For this purpose, they compared the effects of sodium bicarbonate and sodium chloride. Their results showed that hydration with sodium bicarbonate prior to place a person to contrast It is more effective than sodium chloride in preventing contrast-induced kidney failure. The main factor in this study was serum creatinine (20). Sodium chloride like sodium bicarbonate helps the body to absorb fluids in conditions such as diarrhea and severe bleeding in which the body loses fluids, through hydration (30).

Blood transfusion is done when increased blood bilirubin occurs and hemolysis is severe (9). Based on the results of this study it was observed that except for one case, all patients had severe hemolysis and less than 9 mg/ml hemoglobin. Therefore, they took blood transfusions. Received blood volume was similar in both groups and statistically there was no significant difference (P>0.05). Severe hemolysis in both groups with the similar effects indicates that, clinically there was a very little difference between them.

Despite the numerous studies on the complications of bicarbonate (17, 18, 22) in present study, no adverse effects were observed. Although, Aschner et al., (2008) demonstrated that side effects of sodium bicarbonate, such as heart damage and kidney failure in children and metabolic acidosis in animal models is more common (18), but in the present study, any side effects of sodium bicarbonate was not found in children.

Aschner et al., (2008) reported several retrospective studies have showed a strong

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relationship between intracranial hemorrhage and rapid infusion of sodium bicarbonate with high osmolality. It seems that injection speed and osmolality are key factors, and injection of dilute solution of sodium bicarbonate should be done slowly (18). It is likely that osmolality of sodium bicarbonate solution used in the present study and method of injection of solution could be effective in the absence of side effects. However, Masuda et al., (2008) showed that the side effect of sodium bicarbonate in comparison with sodium chloride in chronic kidney disease patients is less in long term. The mortality rates need to find a kidney transplant, dialysis, and death caused by kidney transplant in patients treated with sodium chloride was more (21). The result of the Masuda's study is in contradiction with the results of other studies on the adverse effects of sodium bicarbonate (21) and is in agreement with findings of present study.

Conclusion

Sodium bicarbonate increased the urinary pH more than Sodium chloride, but it was less effective than sodium chloride on the duration of hospitalization. Sodium chloride was considerably effective in shorten the hospitalization duration and taking into account the small clinical difference in received blood volumes, hemoglobin changes and clarification time of UA in terms of hemoglobin, it is suggested that properly, sodium chloride can have a greater impact on the treatment of hemolysis caused by G6PD deficiency. The absence of side effects in both groups can be due to the controlled injection, drugs' concentration as well as the limitation of the study population.

Acknowledgements

We thank all nurses of oncology and emergency departments of Taleghani Children Hospital for sharing their pearls of wisdom with us during the course of this research.

Conflict of interest

There was no conflict of interest.

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