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Study of Transcranial Doppler in Children with Sickle-Cell Anemia in Bandar Abbas Children's Hospital in Period of 2010- 2011

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ABSTRCT: Transcranial doppler is a screening test to detect patients with sickle-cell disease who has high cerebral blood flow velocities. Prophylactic blood transfusion and hydroxyurea recommended for patients with cerebral blood velocities higher than 200cm/m to prevent stroke. It was necessary to have more research to find the effect of hyroxyurea on cerebral blood velocity in these descriptive research 42 patients with sickle-cell disease from 2-14years old were enrolled as cases and 20 healthy children without hematologic disease as controls. Transcranial doppler has been done for both group. Cerebral blood velocity in Medial Cerebral Artery was more in cases in compare to controls. Systolic blood velocity in all right and left cerebral arteries was more in cases in compare to controls. Blood velocity in right and left artery in 78.4 % in cases was more in compare to 8% in controls; It shows the significant difference between cases and control. Higher blood velocity in cases was same as other researches but there was no difference between velocity of blood in right and left artery in compare to other researches. In caseses who has been treated with hydroxyurea blood velocity was less in compare to those who didn't take it which was same as other researches.

Keywords: Hydroxyurea, Sickle Cell Anemia, Trans Cranial Doppler

ORIGINAL ARTICLE

INTRODUCTION

Sickle-Cell disease as the most prevalent hemoglobinopathy affects a special type of protein inside the red blood cells, which is called "hemoglobin", causes them to deform and instead of the rounded red blood cells by smooth wall, sticky and sickle ones are produced. The naming of this disease is due to this as well (Thomas, 2004).

The movement of such these blood cells is difficult through tiny vessels and sometimes causes the vessels' occlusion. As a result, oxygen doesn't arrive to tissues and provides tissue damage and creates some complications such as stroke (Thomas, 2004).

The overall study on sickle-cell disease showed that the prevalence and access of stroke in patients with sickle-cell disease type SS (sickle-cell-SS) is four times greater than in patients with sickle-cell disease type SC (ohene-frempong et al., 1998).

Although vasculopathy of arteries intracranial is considered the greatest cause of stroke in these patients, but the other etiologies, should be considered in young patient (Williams et al, 1997). The other causes of stroke in children, including infections, cardiac emboli, and coagulation disorders such as anti-cardiolipin antibody should be noticed too (Roaeh, 2000).

The incidence of stroke is in 10% of children with sickle-cell disease, which often has the ischemic type and follows stenosis or occlusion of major cerebral arteries such as the internal carotid artery and middle cerebral artery. The stroke is of the major fatal complications of this disease. Comparison between the high incidences of stroke in children with sickle-cell disease and healthy ones, both from the same age group, reveals the role of the previously mentioned disease. The occurrence of stroke without any precaution and creation of prolonged neurological sequel in at least 50% of patients requires serious attention to the prevention and therapeutic interventions in this group of children. Although the periodic frequent transfusion could decrease strokes but, it would not be able to prevent irreversible neurologic damages (Watter et al., 2004).

The children with sickle cell disease could have some type of anatomic and physiologic abnormalities, which involve the central nervous system. Even, it is

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possible that they would be morphologically normal (Powars, 2000).

Nowadays, the extent and in some occasions, severity of tissue damages in these patients and to some extent, access to new diagnostic, prevention and therapeutic method in medicine science field caused the enormous and serious attentions to be paid to this group of diseases, hence promises the more explicit prospects (Persis et al., 2003).

The diagnosis of previous infarctions not observed in CT scan is enabled by MRI images. Transcranial doppler is broadly used in diagnosis of the cerebral arteries pathology. It is obvious that sickle-cell disease is not an exception in this rule and numerous studies have confirmed the ability of this technique in early diagnosis of the risk of stroke (Kandeel et al., 1996). If the velocity of cerebral blood flow increases in patients, they require transfusion that it can prevent a stroke (Thomas, 2004).

Due to high costs, considerable morbidity, the sporadic reports of death, infections, alloimmunization and hemosiderosis of the transfusion, using the alternative treatment methods is inevitably.

Hydroxyurea is the first known drug in treatment of sickle-cell disease and has been used since 1995. This drug causes the decrease of painful crisis and about 50% decrease of acute chest syndrome in these patients. But this drug does not lead to cure of them. Recently, some evidences have been found for the influence of hydroxyurea in stroke numbers of sickle-cell patients (Pakdaman et al., 2005). The other drug is nimodipine, which is a calcium antagonist and used in subarachnoid hemorrhage in adult (Gulbis et al., 2005). Its application has not been confirmed in children with sickle cell disease. In acute phase ischemic strokes in adults without sickle cell disease, the only proven treatment is to use t-PA in early 3 hours (Powars, 2000), but there is no information about its use in children with sickle cell disease.

In many studies, transcranial doppler method has been investigated for early diagnosis of cerebral vascular incidents. For example, in a study conducted in Arakuja region in Brazil, transcranial doppler was performed to survey anterior cerebral artery, posterior cerebral artery and medial cerebral artery and vertebral artery in which the blood flow velocity is the same in right and left arteries for both groups.

In a comparison between these two groups, the blood flow velocity in first group was larger than the second group. Additionally in the second group, velocity was more in females. This study indicated that the blood flow velocity in sickle-cell patients differ from non-hematological group.

In another study conducted by Adams et al in Georgia University in 1998, the purpose of case and control groups study was to decreasing Hbs to less than 30 % of total hemoglobin. Results showed a stroke rate in case group lower than control group patients which was equivalent to92%.Transfusion was the cause of stroke in this group (Mayberg et al., 1994).

Also, in a study conducted by Henrietta Eninfal in Memphis, it was observed that the stroke incidence in before transcranial doppler group was 0.67 per 100 patients annually, while in after transcranial doppler group, it was estimated 0.06 per 100 patients. The transfusion frequency in order to prevent stroke in after transcranial doppler period was increased. The role of transcranial doppler and prophylactic transfusion was shown in the above study. Based on this, it was tried to survey the efficiency of this method in this study too. Therefore, the objective of this study is to determine the result of transcranial doppler in patients 2 through 14 years old with sickle-cell anemia, who were under hydroxyurea treatment.

MATERIALS AND METHODS

The current study was a descriptive-analytic study, which was conducted in 2010-2011 on patients 2-14 years old, their Hbs percent was 50% more than the total hemoglobin, and they were under hydroxyurea treatment. These patients were selected from 137 patients, which hematology group in Bandar Abbas children's hospital diagnosed their disease. The case group was 20 patients and the control group was 20 patients too, that similar to the case group in age distribution. C.B.C test was used to determine hemoglobin and hematocrit of case and control group and blood electrophoresis test was used to determine Hbs level. For case and control groups transcranial doppler was performed as well.

Transcranial Doppler procedure

Transcranial Doppler was done in the same conditions of temperature and posturing (sitting on a chair) for case and control groups. Before transcranial doppler start, an enough time was given to them until their pulse rate and blood pressure would reach a stable condition. The surrounding environment was quietly calm and this provided the possibility of detecting low amplitude signals with high frequency. To perform Transcranial Doppler, DMS apparatus made in France was used. The sedative drugs were not used in transcranial Doppler. To start, at first using sonography gel, carotid of both sides was checked and then through temporal view, Internal Cerebral Artery, Anterior Cerebral Artery, Medial Cerebral Artery and Posterior Cerebral Artery were seen. Vertebral artery from the posterior neck was visible.

For parents described that transcranial doppler is not dangerous to the child then written informed consent was obtained from parents. The inclusion criteria to enter the study were the age in 2-14 years old, Hbs higher than 50% of total hemoglobin including Hbss_Hbsβ _Hbsβ and taking hydroxyurea. The exclusion criteria of the study were the history of stroke or any cerebral vascular

accident, no taken hydroxyurea, Hbs lower than 50% and heterozygous sickle cell anemia (HBAS). After data collecting, the statistical software of SPSS v.17 was used to analyze data. Descriptive statistics such as average, standard deviation and percent were used to data description and in inferential statistics section, T-test was used.

RESULTS

From 42 patients on whom transcranial doppler was done, no patients having the blood flow velocity faster than 200 cm/s. Only in two patients it was intermediately high (170-199 cm/s) which was 4.76% of all of patients and the other ones had normal blood flow velocity. Blood flow velocity of two patients in left Medial Cerebral Artery increases so that in one of them was 170 cm/s and in the other one; it was 187.5 cm/s. The age average of case group was 8.1±3.5 and of the control group was 7.8±3.4. T-Test showed that there was no significant difference between two groups. The average amount of hemoglobin in case group was 8.7±1.4 gr/dl and in control group was 12.7±1 gr/dl. After statistical analysis of data, a significant difference between two groups in amount of hemoglobin is observed ($p<0.001$). In addition, the average hematocrit in case group was 25.51 and it was 39.18 for control group that a significant difference was observed between two groups ($p<0.001$). These values are shown in Table 1**.**

The systolic blood flow velocity in 12 cerebral arteries were compared between male and female in case group that only in left common carotid artery and left Internal Cerebral Artery, there was a significant difference between male and female and in both arteries, the systolic blood flow velocity was lower in females and was $p=0.024$ and $p=0.009$. This result is shown in Table 2.

In another analysis, the patients were divided into 3 groups: fewer than seven, 7-10 and above seven and systolic blood flow velocity was compared for these three groups. The result of studies showed that there was no significant difference among three groups ($p> 0.05$), but by increase of age, systolic blood flow velocity was decreased it was shown in Figure1. In table 3, the average of systolic blood flow in 12 arteries in case and control groups was studied.

Table 1. Evaluation of hemoglobin and hematocrit incase and control groups.

Variable	Group	N	Mean	SD	T	p-value
Hemoglobin	Case	42	8.77	1.48	2.87	p < 0.001
	Control	20	12.78	1.02		
Hematocrit	Case	42	25.51	4.11	2.79	p < 0.001
	Control	20	39.18	4.28		

Table 2. Comparison of indexes Systolic flow rate (cm/S) in brain arteries between male and female of case group

Artery	Sex	N	Mean	SD	T	p-value
CCA-R	Male	21	61.74	20.91	1.33	p >0.05
	Female	21	70.14	27.35		
CCA-L	Male	21	60.63	21.04	2.47	p <0.025
	Female	21	78.64	28.21		
MCA-R	Male	21	81.93	25.30	1.39	p >0.05
	Female	21	80.08	27.59		
MCAL	Male	21	91.40	28.28	1.43	p >0.05
	Female	21	76.63	40.76		
ACA-R	Male	21	54.10	20.80	1.52	p >0.05
	Female	21	54.54	20.96		
ACA-L	Male	21	65.33	27.21	1.32	p >0.05
	Female	21	60.04	23.32		
PCA-R	Male	21	67.76	34.83	1.62	p >0.05
	Female	21	61.05	20.23		
PCA-L	Male	21	72.10	27.50	1.41	p >0.05
	Female	21	61.01	20.08		
ICA-R	Male	21	77.81	23.48	1.32	p >0.05
	Female	21	80.47	21.34		
ICAL	Male	21	58.81	18.83	2.71	p <0.01
	Female	21	77.26	24.52		
ECA-R	Male	21	71.27	23.86	1.68	p >0.05
	Female	21	74.99	23.76		
ECA-L	Male	21	71.04	25.85	1.59	p >0.05
	Female	21	81.57	27.07		

R: Right; L: Left

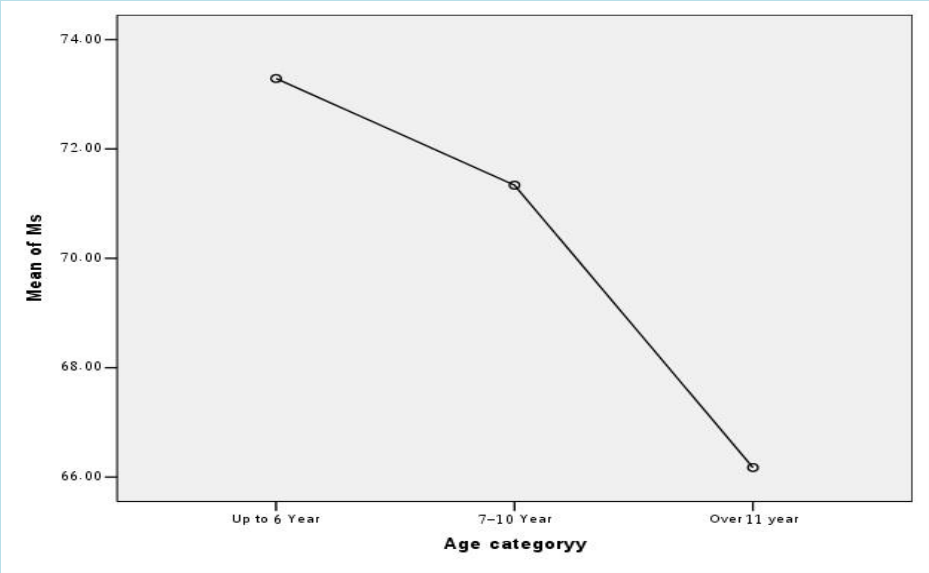

Figure 1. Comparison of mean velocity of blood flow (cm / s) in the three age groups

Table 3. Comparison of indexes Systolic flow rate (cm / S) in brain arteries between case and control groups

Artery	Group	N	Mean	SD	T	p-value
CCA-R	Case	42	65.94	24.42	2.67	p <0.05
	Control	20	38.41	10.07		
CCA-L	Case	42	69.63	26.22	2.59	p <0.05
	Control	20	39.04	08.45		
MCA-R	Case	42	79.14	22.20	2.53	p <0.05
	Control	20	49.70	14.07		
MCAL	Case	42	68.04	23.53	2.39	p <0.05
	Control	20	46.87	16.27		
ACA-R	Case	42	73.13	23.59	2.49	p <0.05
	Control	20	42.71	13.08		
ACA-L	Case	42	76.30	26.68	2.45	p <0.05
	Control	20	45.03	17.47		
PCA-R	Case	42	81.00	26.16	2.70	p <0.05
	Control	20	45.08	11.32		
PCA-L	Case	42	84.02	35.44	2.65	p <0.05
	Control	20	41.57	14.86		
ICA-R	Case	42	54.32	20.63	2.34	p <0.05
	Control	20	62.69	10.62		
ICAL	Case	42	34.20	95.17	2.45	p <0.05
	Control	20	64.41	12.56		
ECA-R	Case	42	38.54	28.33	2.56	p <0.05
	Control	20	66.55	17.77		
ECA-L	Case	42	35.74	24.43	2.52	p <0.05
	Control	20		11.98		

The average of systolic blood flow in case group had the greatest values in left medial cerebral artery , right medial cerebral artery and right internal cerebral artery and in control group the greatest values in right internal cerebral artery , left internal cerebral artery and right medial cerebral artery. The average of systolic blood flow between case and control was separately studied. The blood flow velocity in case is significant more than control ($p< 0.05$).

The systolic blood flow velocity between right and left in common carotid artery, internal cerebral artery, external cerebral artery, anterior cerebral artery, posterior cerebral artery and medial cerebral artery was assessed and the comparison was done between right and left cerebral artery.

According to performed studies in case group, in 54.3% of cases, there is a significant difference between blood flow velocity in right and left sides of cerebral arteries, while this value is 8% for control group ($p<0.05$). The average value of Hbs in case group was 68.21±9.39 %. The minimum value of Hbs and maximum value of total hemoglobin were 52% and 88.4%.

DISCUSSION

In the present study, blood flow velocity in sickle-cell patients is more than hematologic healthy people, which had been shown in many researches before. The obtained finding is consistent with HyderAragao study in which that velocity was greater for case than control group (Hyderoragao et al., 2007).

In study conducted in this center, all of the patients were at least one year under treatment with hydroxyurea, hence the blood flow velocity is significant less than the other patients who were not under treatment with hydroxyurea, while in HyderAragao, it was obviously the blood flow velocity more for patients who are not under that treatment than studied patients (Hyderoragao et al., 2007).

In the present study, blood flow velocity has had decrease by age increase in three groups of patients including fewer than seven, 7-10 and above seven. The findings of Adams and Henrietta Eninfal studies have shown that the maximum age of stroke prevalence is 4 years (Henrietta et al., 2004; Adam et al., 2011). Although this decrement was not significant but it partially could justify the higher blood flow velocity in 2-6 years group. The findings of present study showed that the average of blood flow velocity in medial cerebral artery was higher and this result had been reported in studies of Adams and Henrietta Eninfal, as well.

Generally, the results of current study showed that transcranial doppler diagnosis method for early diagnosis of cerebral vascular accidents has an almost appropriate efficiency in sickle-cell patients in the range of 2-14 years old. It is suggested that in future studies, application and efficiency of this method in other age groups and as an alternative method for transfusion would be studied.

REFERENCES

Adam, J, Cimckie S, Lewis HSU, et al. (2011). Prevention of first stroke by transfusion in children with sickle cell Anemia and Abnormal results on Transcranial Doppler. Nejm.

Gulbis B. Habermann D, Dofour D, Christopher et al. (2005). Hydroxyurea For Sickle cell disease in children and for Prevention of Cerebrovascular events: the Belgian experience. Blood. April, 1,105(7): 2685-90.

Henrietta. Enninful-Eghan-rene. H. more-New (2004) England medicine.

Hyderoraga de maleojoseAugusto.S.Barre to, Roberto Cesar Evaluation of brain blood flow parameters in children of Aracaju Brazil -2007.

Kandeel A.Y., Zimmerman R.A., Ohene-Frempong K. (1994). Comparison of Magnetic Resonance Angiography and conventional angiography in sickle cell disease: clinical sign *facant* and reliability. Neuroridiol. 36: 409-16.

Mayberg MR, Batjer HH, Dacey R, et al. guidelines for management of aneurismal subarachnoid hemorrhag, stroke; 25: 231-20.

Ohene-frempong K, Lveintersy, Sleeper LA et al. (1998).cerebrovascular accidents in sickle cell disease: rate and risk factors, Blood; 91: 988-94.

Pakdaman, H. et al. (2005). Transcranial Doppler, principles and applications, Tehran: Arjmand Publications.

Persis Y. Amrolia, Alemida, Davis Irene. A.R. Roberts, (2003). Therapeutic challenges in childhood sickle cell disease, British journal of hematology, 2003, 120, 725-736.

Powars D.L. (2000). Management of cerebral vasculopathy in children with sickle cell disease. Br J Haematol; 108: 666-78.

Roaeh E.S. (2000). Stroke in children. Carr Trat Options Neural; 2:225-304.

WatterQ.Broddley Neurology in clinical Practice, (2004), (660-661).

Williams L.S. Garg B.P., Cohen M. et al. (1997). Subtypes of ischemic stroke in children and young adults neural 49: 1541-5.