Advances in Bioresearch
Adv. Biores., Vol 6 (5) September 2015: 211-217
©2015 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
ICV 7.20 [Poland]

Advances in Bioresearch

ORIGINAL ARTICLE

Evaluation of Tricuspid Regurgitation Jet Velocity in Children with Sickle Cell Disease in Iran 2012-2013

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ABSTRACT
Sickle cell is an autosomal recessive disease that leads to numerous, hemolysis, acute and chronic vascular occlusive episodes. In several studies the relationship between the degree of hemolysis and markers of pulmonary hypertension in patients with sickle cell disease has been observed. Elevated tricuspid regurgitation is associated with increased mortality. In a case-control study, 70 patients with sickle cell referred to Children's Hospital Hematology unit of BandarAbbas were studied. The study population consisted of individuals 2 to 14 years have been based on hemoglobin electrophoresis for diagnosis of disease. Patients were compared with 70 subjects in control group who were matched for age and sex. Then the full blood examination and thoracic echocardiography was done and tricuspid regurgitation velocity was measured. Tricuspid regurgitation velocity rates more than 2.5(m/s) was considered as increased. Data was analyzed by SPSS software version19.The results showed that the average TRV in group with sickle cell disease in boys and girls and in the total sample was higher than control group. The systolic blood pressure was not significantly different between the two groups (case and control) but in terms of diastolic blood pressure, hemoglobin, WBC and O2sat and tricuspid regurgitation velocity difference between the two groups (case and control) was significant. In cases group, between two groups, that had TRV above and below 2.5 meters per second, there was significant differences in age and no significant in other variables. Overall, the results of this study showed that TRV affected by diastolic blood pressure, hemoglobin, WBC and O2 sat.
***Key word**: sickle cell, tricuspid regurgitation velocity, pulmonary hypertension*

Received 12.04.2015 Accepted 07.09.2015

How to cite this article:
Mohammad Ali M, Shahrokh R, Zainab E, Abdol Majid N, Shahram Z. Evaluation of Tricuspid Regurgitation Jet Velocity in Children with Sickle Cell Disease in Iran 2012-2013. Adv. Biores., Vol 6 [5] September 2015:211-217. DOI: 10.15515/abr.0976-4585.6.5.211217

INTRODUCTION

Sickle cell is a recessive autosomal disease in which valine replaces glutamine in the sixth position on the beta hemoglobin chain causing mutation in S hemoglobin that is polymerized after losing oxygen. This is the main event that leads to hemolysis, episodes of vascular blockage, and numerous severe and chronic complications [1]. In cross sectional studies, relationships have been observed between the degree of hemolysis and the markers of pulmonary artery pressure in sickle cell patients [2, 3]. Increased velocity of tricuspid regurgitation is revealed by echocardiography in more than one third of people with sickle cell disease, which is accompanied by increased systolic pressure of the pulmonary artery and a rise in mortality rate [4]. Increased velocity of tricuspid regurgitation and left ventricular diastolic dysfunction develop in children suffering from sickle cell disease, but their clinical importance is unknown. It is not clear whether screening and intervention for these complications must start in childhood [3, 4, and 5].
Pulmonary hypertension is a very dangerous and life-threatening complication that is revealed in echocardiography in which the diagnosis criterion is based on the velocity of blood flow back across the tricuspid valve defined as more than 2.5 meters per second, which is equivalent to the minimum pulmonary artery systolic pressure of 30 millimeters of mercury [6].

Age, gender, race, type of sickle cell disease, episodes of sickle cell crises, acute chest syndrome, hemoglobin level, asthma, and history of cardiovascular disease are among factors affecting TRV [6]. Many studies have been conducted in this regard, a few of which will be mentioned here. Colombatti et al. [7] carried out a study on mainly African children (with the average age of 6.2 years) and found the prevalence of TRV of 2.5 m/sec, which was accompanied by acute chest syndrome, to be 21.6 percent or higher.

In an analysis of 339 (2-20 year-old) sickle cell patients by Gordeuk et al. [9], it was observed that in 11 percent of them the TRV had risen to more than 2.5 meters per second. In a prospective study Dham et al. conducted, 403 adult sickle cell patients were evaluated by using echocardiography and it was found that in 96 (24 percent) of them TRV was 2.5 m/s [8].

Gordeuk et al. conducted another research to study the consequences of increases in the hemolysis rate, of rising TRV, and of left ventricular dysfunction in 160 children (average age of 13 years and age range of 3-20) with hemoglobin S disease by following up the condition of these patients for an average duration of 22 months (range of 9-35 months). They observed that, in 14.1 percent of these patients the TRV was 2.6 m/s or more, and that these high TRV values were more prevalent in children being treated by chronic blood transfusion. Interestingly, they noticed increases (9.23 or more) in E/Etdi of the mitral valve of 7.7 percent of the children, which indicated rises in the right ventricular filling pressure [9]. Gordeuk et al. [9] found a significant independent correlation between more hemolytic markers and less hemoglobin oxygen saturation with higher TRV. Increases in hemolytic markers from the average value were accompanied by nine-fold rises in the risk of the start of new high TRV with time and by increased risk of higher follow-up E/Etdi of the mitral valve. Although both biomarkers are predictors independent of high TRV (because of the low prevalence of high E/Etdi), hemolytic markers, as more important risk factors, are better predictors for identifying people in danger of a new start of pulmonary hypertension revealed by using Doppler flow index [9].

Considering what was said above, and because of high rates of mortality that follows increases in TRV in sickle cell patients, we decided to study TRV in sickle cell patients of Hormozgan Province in 2012-2013. Our purposes were to reduce the mortality rate, to improve the quality of life of these patients, and to prevent a rise in the economic burden imposed on the society.

METHODOLOGY

The statistical population in this study consisted of all sickle cell patients visiting the hematology ward of the Children's Hospital in Bandar Abbas, and the studied sample was selected from this population. In this case-control study, 70 sickle cell patients visiting the hematology ward of the Children's Hospital in Bandar Abbas were selected using the simple random sampling method to be studied. These 2-14 year old patients had been diagnosed with sickle cell disease using the hemoglobin electrophoresis test. They were compared with the 70 people in the control group who were of the same age and gender as the case group.

General information such as age, gender, the length of time passed since the disease was diagnosed, the number of times the patient was hospitalized after sickle cell crises, the incidence of acute chest syndrome, history of cardiovascular disease, and history of splenectomy was inquired, and the answers were recorded.

Full blood count test, peripheral blood smear, lactate dehydrogenase test, bilirubin test, reticulocyte count, liver enzymes test, and urine test were conducted, chest echocardiography was performed, and tricuspid regurgitation velocity (TRV) was measured for all those who participated in the study.

Participants were divided into the two groups of normal TRV (less than 2.5) and increased (abnormal) TRVs (higher than 2.5). Patients with heart conditions such as pulmonary stenosis or right ventricular outflow tract obstruction were excluded from the study.

Information collected on patients was analyzed by employing the statistical software SPSS19. Before the analysis, the normality of the data was tested using the Kolmogorov-Smirnov test. Mean descriptive statistics, standard deviations, frequencies, and percentages, plotting graphs and diagrams were used for descriptive statistics, and the chi-square test, t-test, and ANOVA were employed for the inferential statistics. It must be noted that the level of significance of less than 0.05 was considered in all analyses.

RESULTS

Seventy children with sickle cell disease (45, 64.3 percent, boys and 25, 35.7 percent, girls) with the average age of 7.41 years were compared with 70 healthy children (40, 57.14 percent, boys and 30, 42.86 percent, girls) with the average age of 7.19 years. They were divided into age and gender groups and

compared with respect to the velocity of blood flow back across the tricuspid valve. Both case and control groups were classified into three age groups.

The average TRV was higher in the case group (boys, girls, and the whole group). The t-test showed that the two groups were significantly different ($p < 0.05$) (Tables 2-4). Table 3 presents results of analysis of the variables in the case and control groups.

We made a scatter plot of the two variables of tricuspid regurgitation jet velocity (m/sec) and O2 sat (%) to find if they were related. Since both are quantitative variables, the Pearson coefficient between them was calculated (which was 0.80 and significant at the 0.001 level). It must be mentioned that the normality of the data was tested and confirmed using the Kolmogorov-Smirnov test before analyzing it.

The calculated chi-square value was significant at the level of less than 0.05, which shows that there was a relationship between the age of the patients and the velocity of blood flow back across the tricuspid valve in these patients

Table 1: Comparison of the case and the control groups with respect to age

Age group	Number (case)	Number (control)
2-6 years old	23	24
6-10 years old	27	28
10-14 years old	20	18
Total	70	70

Table 2: Results of comparison of TRV values with respect to gender

Gender	Group	Number	Average ± standard deviation	T	Df	p-value
Boys	Case	45	2.08 ± 0.58	2.21	68	0.041
	Control	40	1.80 ± 0.51			
Girls	Case	25	2.12 ± 0.38	2.14	68	0.044
	Control	30	1.82 ± 0.44			
Total	Case	70	2.10 ± 0.39	2.23	138	0.001
	Control	70	1.81 ± 0.46			

Table 3: Comparison of clinical and laboratory findings in the case and control groups

Variable	Case	Control	P
Systolic blood pressure (mm Hg)	108 (100-118)	109 (103-122)	0.08
Diastolic blood pressure (mm Hg)	63 (54-72)	65 (58-74)	0.05
Hemoglobin (g/dl)	8.16 (3.5-12)	11.26 (11.1-12.8)	0.001
White blood cell (* 10^3 / L)	12.87 (2.9-26.7)	5.8 (4.8-7.6)	0.001
O2 sat (%)	97.92 (93-100)	99.8 (99-100)	0.001

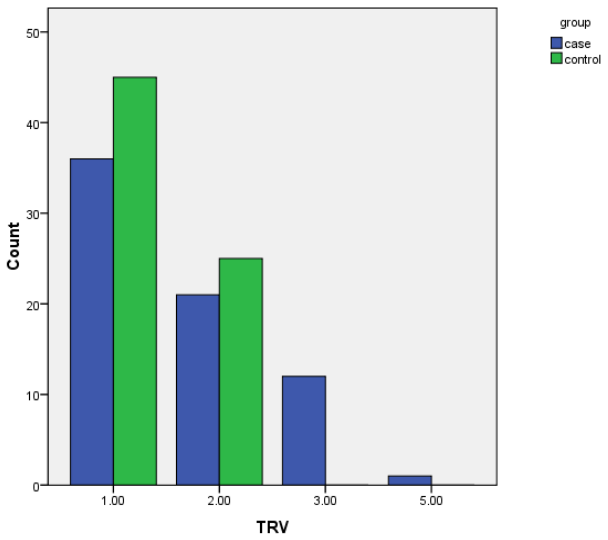

Diagram 1: TRV values (m/sec) in the case and control groups

Table 4: Clinical and laboratory findings related to the case group

	N	Minimum	Maximum	Mean	Std. Deviation
Years after the diagnosis of the disease	70	1	13	4.81	3.46
Number of times of hospitalization	70	1	20	4.40	4.26
White blood cell (*$10^3/L$)	70	2.9	26.70	12.87	5.94
Hemoglobin (g/dl)	70	3.5	12	8.16	1.93
LDH	70	105	2357	1016	414.64
Total bilirubin (mg/dl)	70	0.40	4.9	1.94	0.79
SGOT (U/L)	70	20	125	52.60	19.83
SGPT (U/L)	70	10	139	29.44	26.62
Reticulocyte (%)	70	1	3.9	2.08	0.56
O2 sat (%)	70	93	100	97.92	1.66
TRV (m/sec)	70	1	5	2.10	0.519

Table 5: Frequency and percentage of clinical and laboratory findings in the case group

Variable		Frequency	Percentage
TRV (m/Sec)	Below 2.5	57	81.4
	Over 2.5	13	18.6
Incidence of acute chest syndrome	Zero	54	77.1
	Once	9	12.9
	Twice	7	10
Splenectomy	Yes	3	4.3
	No	67	95.7
Transfusion	Yes	38	54.3
	No	32	45.7
Taking hydroxyurea	Yes	56	80
	No	14	20
Urine test	Normal	64	91.4
	Abnormal	6	8.6

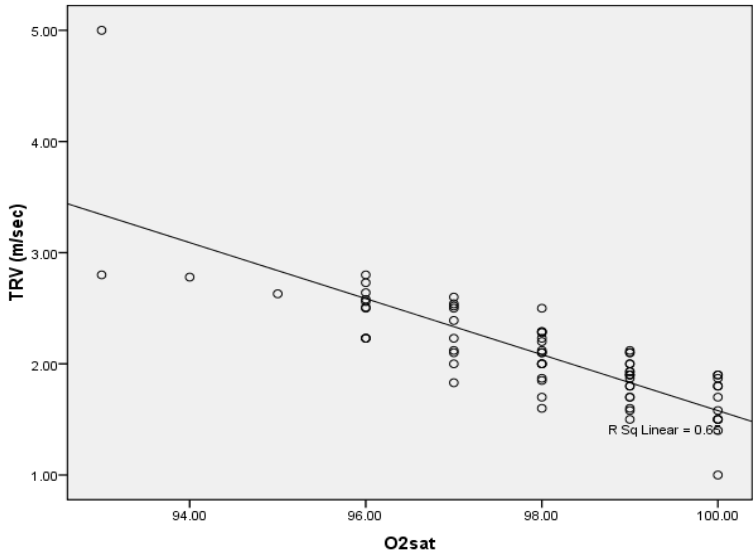

Diagram 2: Relationship between tricuspid regurgitation jet velocity (m/sec) and O2 sat (%)

Table 6: Velocity of blood flow back across the tricuspid valve in patients based on age in the case group

Age group	2-4 years	6-10 years	11-14 years	Total	Chi-Square	P
TRV (m/sec) < 2.5	26	19	12	57	10.04	0.007
TRV (m/sec) > 2.5	1	4	8	13		
Total	27	23	20	70		

Table 7: Velocity of blood flow back (across the tricuspid valve) in patients according to their gender in the case group

Gender	Boys	Girls	Total	P
TRV (m/Sec) < 2.5	37	20	57	0.52
TRV (m/Sec) > 2.5	8	5	13	
total	45	25	70	

Table 8: Velocity of blood flow back (across the tricuspid valve) in patients based on the time passed since the disease was diagnosed in the case group

Time past since the disease was diagnosed	Less than 5 years	5-8 years	More than 9 years	Total	P
TRV (m/sec) < 2.5	38	8	11	57	
TRV (m/sec) > 2.5	5	3	5	13	0.16
Total	43	11	16	70	

Table 9: Velocity of blood flow back (across the tricuspid valve) based on the number of times of hospitalization after crises in the case group

Number of times of hospitalization after crises	Less than 4	5-8	More than 9	Total	P
TRV (m/Sec) < 2.5	36	12	9	57	
TRV (m/Sec) > 2.5	4	4	5	13	0.07
Total	40	16	14	70	

Table 10: Velocity of blood flow back (across the tricuspid valve) in patients based on the incidence of acute chest syndrome in the case group

Incidence of acute chest syndrome	Zero	Once	Twice	Total	P
TRV (m/Sec) < 2.5	44	6	7	57	
TRV (m/Sec) > 2.5	10	3	Zero	13	0.23
Total	54	9	7	70	

Table 11: Velocity of blood flow back (across the tricuspid valve) based on the type of disease in the case group

Type of disease	Sickle cell trait	Sickle cell-thalassemia	Sickle cell disease	Total	P
TRV (m/Sec) < 2.5	16	3	38	57	0.23
TRV (m/Sec) > 2.5	2	1	10	13	
Total	18	4	48	70	

Table 12: Comparison of blood hemoglobin level of patients in the two groups of TRV values of less than 2.5 and more than 2.5

Hemoglobin level	Mean	Standard deviation	Minimum	Maximum	DF	T	P
TRV (m/sec) < 2.5	8.19	2.02	3.5	12	68	0.25	0.18
TRV (m/sec) > 2.5	8.03	1.56	4	9.70			
Total	8.16	1.93	3.5	12			

Table 13: Velocity of blood flow back (across the tricuspid valve) based on the transfusion situation in the case group

Transfusion situation	Received transfusions	Did not received transfusions	Total	P
TRV (m/Sec) < 2.5	28	29	57	0.18
TRV (m/Sec) > 2.5	10	3	13	
Total	38	32	70	

Table 14: Velocity of blood flow back (across the tricuspid valve) in patients in the case group based on taking hydroxyurea

Situation with regard to taking hydroxyurea	Taken	Not taken	Total	P
TRV (m/sec) < 2.5	45	12	57	0.64
TRV (m/sec) > 2.5	11	2	13	
Total	56	14	70	

DISCUSSION AND CONCLUSION

In our research, elevated tricuspid regurgitation velocity (> 2.50 m/sec) was studied in sickle cell patients, and it was found that its prevalence and frequency were 18.5 and 13, respectively. Similar results have also been reported in various studies such as those conducted by Gordeuk et al. in 2009 and Caterina *et al*. [10] and by Pashankar *et al*. [11], in which they found the prevalence of 11, 24, and 30%, respectively.

Our results showed that there were no significant differences between the two groups with regard to the variables of age and gender, although in the case group and regarding the variable of age, TRV > 2.5 (m/sec) was observed more frequently (8 cases) in the age group of 11 to 15 years. This finding is in agreement with that found by Caterina *et al*. in 2008, who reported TRV > 2.5 (m/sec) in the age group of 6 to 17 years of age (with the median of 13 years). The two groups were not significantly different in systolic blood pressure (in mm Hg).This while They differed significantly in the variables of diastolic blood pressure, hemoglobin, WBC, O2 sat, and TRV (and these significant differences have been reported in various studies). For example, in the study Caterina *et al*. conducted in 2008, it was found that diastolic blood pressure in the case group was significantly higher than that of the control group (and in our research this difference was significant too).

Another finding of our study was that the differences in TRV between the case and the control groups were significant, a finding that was also confirmed in a study Pashankar et al. conducted in 2008.

Comparison of the levels of Hemoglobin in the case and control groups revealed that the differences between the two groups were significant. Findings of Kato et al. [12] confirm the present results. They found that the hemoglobin level in the case group was significantly lower than that in the control group and, in our study too, the level of hemoglobin in the case group in those with TRV < 2.5 (m/sec) was higher compared to those with TRV > 2.5 (m/sec). The differences between the two groups in O2 sat were significant, and this was confirmed in the study Gordeuk et al. carried out in 2009 in which an independent and significant correlation between low O2 sat and high TRV was reported [13].

Based on the results we obtained concerning transfusion, there was no relationship between transfusion and the velocity of blood flow back across the tricuspid valve. This is in contrast with the findings of Machado *et al*. [14] in whose study this relationship was significant. The reason for this difference is that in the study Machado et al. conducted the number of units of blood transfusion during their lifetime was also considered, and they concluded the chronic transfusion therapy could prevent rises in TRV in most patients, while we did not study the number of received units of blood transfusion in our research.

Lack of a relationship between taking hydroxyurea and velocity of blood flow back across the tricuspid valve was another of our findings. This issue was also dealt with in the research Gordeuk et al. [13] conducted, and in which they did not find a significant relationship between taking hydroxyurea and velocity of blood flow back across the tricuspid valve. It is worth noting that in their study the comparison between the two groups was performed at TRV higher than 2.5, while we did not conduct this analysis because of the low volume of the sample with TRV higher than 2.5 [13].

In general, our results indicated there were no significant differences between the two groups regarding the variables of age and gender. There were no significant differences between the two groups in systolic blood pressure either, while they showed significant differences in the variables of diastolic blood pressure, hemoglobin, WBC, O2 sat, and tricuspid regurgitation velocity.

Based on obtained results in our research, we suggested that:

1. More studies are conducted to determine whether children and adolescents with sickle cell disease will eventually develop pulmonary hypertension in adulthood.
2. In future studies, left ventricular diastolic dysfunction and mitral valve E/tissue Doppler E ratio are investigated too, because left ventricular diastolic dysfunction is related to mortality in sickle cell patients and may raise pulmonary artery blood pressure.

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