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ORIGINAL ARTICLE

Lower Transcranial Doppler Flow Velocities in Sickle Cell Anemia Patients on Hydroxyurea: Myth or Fact

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Abstract Transcranial Doppler (TCD) detects stroke risk in patients with sickle cell anemia (SCA). Hydroxyurea therapy has the ability to induce increased levels of fetal hemoglobin in sickle cells thus decreasing tendency for red cell sickling. This study aimed to evaluate TCD findings in SCA patients on hydroxyurea and correlate the time-averaged mean velocity (TAMV) with their hematological parameters. Forty SCA patients of both sexes, aged 16–22 years with no history of stroke were screened with TCD for an elevated TAMV, divided into: Group T (20 patients on blood transfusion); and Group H (20 patients on daily hydroxyurea). For all, full medical history, clinical examination, hemoglobin, hematocrit, leukocytes, platelets, fetal hemoglobin and sickling test, in addition TCD to describe the pattern of cerebral blood flow abnormalities were done. TAMV in all cerebral arteries were significantly higher in Group T than Group H, the highest TAMV (147.5 ± 57.09 cm/s) was found in the right middle cerebral artery and correlated negatively with hematocrit in Groups H ($P < 0.001$). There were 2 (10%) abnormal TAMV results and 5 (25%) conditional in Group T, while all results were normal in Group H. Hydroxyurea therapy may lower TCD velocities and prevent the risk of primary stroke in SCA patients.

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Introduction

Sickle cell disease (SCD) is an autosomal recessively inherited β-hemoglobinopathy causing an abnormal hemoglobin (HbS) to be expressed in the erythrocyte, the homozygote SS form is known as SCA [1]. In the S-beta globin gene, a normal codon (GAG) is replaced by another (GTG), resulting in exchanging the sixth amino acid of the beta globin. This exchange of glutamic acid for valine causes polymerization of hemoglobin S, when exposed to media with low oxygen tension leads to sickling of red blood cells. This process is responsible for most of the clinical manifestations of SCD [2]. Stroke is one of the clinical complications of SCD [3]. About 5–10% of patients with SCA present stroke by the age of 20 years [4]. Cerebral infarction results from occlusion/stenosis of large arteries supplying the brain. The distal intracranial portions of the internal carotid artery and the proximal middle cerebral artery are particularly prone to stenosis, which can be detected by TCD [5]. TCD is a crucial investigation that can reveal elevated cerebral arterial flow velocities [6]. TCD studies measure flow velocity within the large intracranial arteries, which are the vessels most often involved in sickle cerebral vasculopathy and stroke [7]. It is useful because it is painless, requires no sedation, noninvasive, easy to perform and relatively inexpensive [8]. It is recommended as a routine screening test for patients with SCA, it enables early detection of arterial abnormalities, which is important for primary stroke prevention [9]. Adams et al. [5] conducted several studies using TCD to demonstrate the usefulness

of this examination for evaluating stroke risk. Several factors influence the blood flow velocities obtained through TCD, of which hematocrit level, leukocyte and platelet counts [10]. The current standard therapy of monthly blood transfusions to reduce stroke risk can lead to problems such as antibody formation and iron overload, which are recognized as a source of morbidity in SCA patients. Hydroxyurea (HU) is considered as a possible alternative to chronic transfusions for secondary stroke prophylaxis in SCD patients, it acts by several underlying mechanisms [6]. It increases HbF levels, possibly because it is cytotoxic, and this toxicity causes regeneration of erythrocytes, increases hemoglobin, with a decrease in Hb S [11]. HU has been reported to be effective in improving survival and reducing morbidity in some SCD patients. The clinical outcomes include reduction in frequency of painful episodes, acute chest syndrome, transfusions and hospitalization, with no significant toxicities [12]. HU therapy is monitored by a number of laboratory parameters which include increased HbF levels, mean corpuscular volume, and reduction in WBC count. It has been found to be effective in the prevention of brain injury due to cerebrovascular disease [13].

In this study our aim was to evaluate the results of TCD examination in SCA patients on hydroxyurea therapy, and correlate TAMV with the hematological parameters.

Patients and Methods

This was a single-center observational cross-sectional study on 40 patients with SCA, their age ranged 16–22 years, and had no previous clinical diagnosis of stroke or acute crises. Patients refused to undergo TCD examination were excluded. Participants were already on transfusion or hydroxyurea therapy with variable time periods before starting the study and we just observe the difference between the two groups. The patients divided into two groups; Group T (transfusion group) received monthly transfusions to maintain sickle hemoglobin level lower than 30%, Group H (hydroxyurea group) received oral hydroxyurea 20 mg/kg per day. Patients were invited to participate in the study after getting informed consent and the steps and aim of the research were explained to participants. The patients were recruited from clinical hematology unit, Internal Medicine department, Assuit University Hospital and Health Insurance, Assiut, Egypt from January 2016 to October 2016.

Laboratory blood tests including hemoglobin, hematocrit level, leukocyte and platelet counts, hemoglobin S assay by means of hemoglobin electrophoresis and fetal hemoglobin assay.

TCD Screening Protocol

TCD studies were performed in the Department of Radiology Assuit University Hospital. All TCD exams were performed by radiologist. With the patient in the supine position, a 3–5 MHz hand-held convex probe of Logic P6 Pro GE machine was placed in the temporal region of the scalp Using right and left temporal approaches. By manipulating probe angulation, probe position and the depth setting of the instrument, the ultrasound sample volume was placed on major arterial segments of the circle of Willis. The TAMV were measured in the middle cerebral arteries, the internal carotid arteries, the anterior cerebral arteries, and the posterior cerebral arteries in centimeters per second. Multiple measurements were taken at varying depths on either side and for each vessel, between 40 and 60 mm. The highest recorded mean velocity for each artery was assumed to be the most representative and this was recorded as the time-averaged mean velocity (TAMV). All the measurements were recorded. All TCD studies were classified based on the highest TAMV in the ICA or MCA based on STOP criteria as normal (<170 cm/s), conditional (170–199 cm/s), and abnormal (200 cm/s or higher). Studies where readings were unable to be obtained in the ICA and MCA bilaterally were classified as inadequate, unless one side was clearly abnormal.

Statistical Analysis

The data obtained was statistically analyzed using SPSS software data analysis program version 17. Non parametric tests were used due to small sample size: Mann–Whitney test was used to compare means of quantitative variables while Fisher exact test was used to compare percents of qualitative variables, spearman correlation coefficient was also used, P value <0.05 was considered to be statistically significant.

Results

40 patients (22 male and 18 female) with SCA were studied. 20 patients as Group T (transfusion group) and 20 patients as Group H (hydroxyurea group). There were no statistically significant differences as regard age and sex between the two groups, but there were a statistical significant increase of (Hb level, hematocrit, MCVand Hb F) in Group H than Group T ($P = 0.001$, 0.002, 0.009 and 0.001) respectively, while no significant differences as regard total WBC count and platelet count (Table 1).

Table 1 Demographic and hematological parameters of 40 patients with sickle cell anemia

Variables	Group T on transfusion (n = 20)	Group H on hydroxyurea (n = 20)	*P* value
Age, year	18.05 ± 1.1	17.75 ± 0.85	NS
Sex: male/female	12 (60%)/8 (40%)	10 (50%)/10 (50%)	NS*
Hb, g/dl	7.4 ± 0.8	9.3 ± 0.8	0.001
Hematocrite, %	21.3 ± 3.6	24.8 ± 3.1	0.002
MCV, fL	84.8 ± 7.6	92.6 ± 10.03	0.009
HbF, %	10.85 ± 2.3	23.1 ± 7.3	0.001
WBC × 10^3/mm^3	8.6 ± 2.6	9 ± 3.7	NS
Platelet count × 10^3/mm^3	267.3 ± 65.9	283.3 ± 65.3	NS

Mann–Whitney test was used * Fisher exact test was used

NS non significant, *Hb* hemoglobin, *MCV* mean corpuscular volume, *HbF* fetal hemoglobin, *WBC* white cell count

TAMV in cm/s were statistically higher in the major intracranial arteries in Group T than Group H. The highest velocities in each patient were recorded in the middle and posterior cerebral arteries (Table 2).

TAMV on TCD studies, among 20 patients on transfusion, 13 (65%) patients had normal velocities TAMV < 170 cm/s, 5 (25%) patients had conditional velocities TAMV > 170 cm/s, while 2 (10%) patient had an abnormal TAMV > 200 cm/s (TAMV of 293.2 and 240.8 cm/s). None of Group H patients showed abnormal TCD velocities (Table 3; Fig. 1).

No evidence of clinical stroke was identified in either treatment group. Vaso-occlusive pain was the most common adverse event in both groups, 3 (15%) patients in Group H and 5 (25%) patients in Group T.

This study showed a significant negative correlation between hematocrit (r = −0.818, $P = 0.001$) and TAMV in Group H. There was no correlation with total WBC count, hemoglobin level, fetal hemoglobin percentage or total platelet count. None of the hematological parameters were significantly correlated with TAMV in Group T (Table 4).

These results suggest that hydroxyurea treatment could decrease time-averaged mean velocities in SCA patients.

Discussion

Stroke is a significant cause of morbidity and mortality in SCD [14]. It occurs in 10–15% of homozygous patients under the age of 10 years [15]. The risk is higher in patients with low baseline hemoglobin, low fetal hemoglobin, high white blood cell count, Hb SS disease and could be candidates for early and aggressive therapy with disease modifying agents [16]. TCD is a procedure commonly used to screen individuals with the major hemoglobin S diseases. Flow velocities above 200 cm/s have been shown to identify patients at elevated risk for cerebral infarction [17] and is an indication for starting hypertransfusion therapy [18]. Noteworthy, the standard therapy of monthly blood transfusions to reduce stroke risk is not without risks, but added more risks, hence, the need for close monitoring and prompt iron chelation when indicated [19]. The estimated mean annual cost of hypertransfusion

Table 2 Flow velocities in the major intracranial arteries in 40 patients with SCA on TCD studies

Artery	Time-averaged mean velocities (TAMV) in cm/s								*P* value
	Transfusion (n = 20)				Hydroxyurea (n = 20)				
	Minimum	Maximum	Mean	SD	Minimum	Maximum	Mean	SD	
Right ICA	100.4	205.8	131.7	41.13	99.4	112.2	105.1	3.4	0.006
Left ICA	99	206.2	131.2	41.36	101.6	114.6	106.1	3.6	0.01
Right MCA	100.2	293.2	147.5	57.09	102.6	120.4	110.4	4.4	0.006
Left MCA	102.2	210.8	135.8	40.6	104.4	120.4	110.98	4.02	0.01
Right ACA	96.6	200.5	127.1	42.5	96.6	103.8	100.1	2.04	0.007
Left ACA	96.4	202.3	127.4	42.55	96.3	104.6	100.1	2.2	0.007
Right PCA	106.2	203	131.1	36.7	102.6	114.4	109.4	3.1	0.012
Left PCA	106.4	207	135.2	39.13	102.4	115.4	109.1	3.6	0.005

Mann–Whitney test was used

TCD transcranial Doppler, *TAMV* time-averaged mean velocity

Table 3 Pattern of TCD abnormalities in 40 patients with sickle cell anemia

Risk classification	On transfusion (Group T) Number (%)	On hydroxyurea (Group H) Number (%)	*P* value
RtMCA, cm/s			0.01
Normal n (%)	13 (65%)	20 (100%)	
Conditional n (%)	5 (25%)	0 (0%)	
Abnormal n (%)	2 (10%)	0 (0%)	
Lt MCA, cm/s			0.02
Normal n (%)	13 (65%)	20 (100%)	
Conditional n (%)	5 (25%)	0 (0%)	
Abnormal n (%)	2 (10%)	0 (0%)	
Rt PCA, cm/s			0.012
Normal n (%)	14 (70%)	20 (100%)	
Conditional n (%)	5 (25%)	0 (0%)	
Abnormal n (%)	1 (5%)	0 (0%)	

Fisher Exact test was used

Normal TAMV: <170 cm/s; conditional TAMV: between 170 and 200 cm/s; abnormal more than 200 cm/s

in SCD patient is about 3276 US Dollars, also, treatment of iron overload increased the cost [20]. Currently, HU is the only disease-modifying therapy approved for SCD. It is efficacious in children and adults; with an increase in Hb F%, reduction in hospitalizations and pain crises. Hence, there is great interest in understanding more about its use in treating patients with SCA [21]. More controlled multi-center trials on the use of hydroxyurea would be extremely valuable in determining the efficacy of this drug in primary and secondary stroke prevention, particularly in Africa where blood is not readily available, quite expensive, and transfusions are associated with a potential risk of transmission of infections [22]. TWiTCH which is the first Phase III randomized clinical trial compared standard therapy of monthly erythrocyte transfusions with daily HU, for children with elevated TCD velocities and high risk of stroke, they reported that HU has a similar benefit as transfusion [23]. Zimmerman et al. [8] evaluated the effect of HU on TAMV, reported a statistically significant decline in TCD velocities.

However, it is better to prevent stroke than to treat it. So, these data urge us to evaluate TCD cerebral blood flow velocities comparing hydroxyurea therapy versus blood transfusion for prevention of primary stroke in sickle cell patients.

Evidence for primary stroke prevention was limited to observational data. Three studies found decreased stroke rates in those administered hydroxyurea compared with no treatment [24–26].

Hydroxyurea, the only medication approved as a disease-modifying agent by the United States Food and Drug Administration and the European Medicines Agency, and is probably associated with decreased mortality among children with SCD. It is usually under-used, especially in developing countries [26, 27]. Ware et al. [23] stated that, HU lower TCD velocities, which lower the risk of stroke. These data support the results of the current study. Our results showed that, patients receiving HU therapy had lower TCD velocities, these results were in agreement with [8, 28] who found that, patients receiving HU had reduced TCD velocities.

Our results were also in concord with the study by Kratovil et al. [29] who assessed the effect of HU on TCD velocities, reported lower velocities in comparison with no HU. Also, Gulbis et al. [30] which stated that, HU may decrease risk of primary stroke in patients with SCD. Platt [15] concluded that, HU therapy reduces CBF, though less effective, HU maybe considered an alternative to chronic transfusion therapy, where transfusion is not feasible. Also with [31] who reported that HU appears to significantly reduce TCD velocities in Nigerian patients with SCA and elevated velocities with beneficial effect on the hematological profile, he added HU may provide an effective approach to primary stroke prevention, particularly in Africa.

This study showed a higher hematocrit percent was associated with lower TAMV in SCA patients. This was consistent with the findings of [8, 20, 32] which reported an association between decline in TCD velocities and increase in Hct percent in their patients while on HU therapy, and with [33] who stated that TCD values were inversely correlated with the hematocrit. Moreover, many other studies on HU-treated patients have shown the same findings [8, 34]. These results support the results of the present study.

Our study showed 5 (25%) patients had conditional velocities, TAMV > 170 cm/s, while 2 (10%) patients had

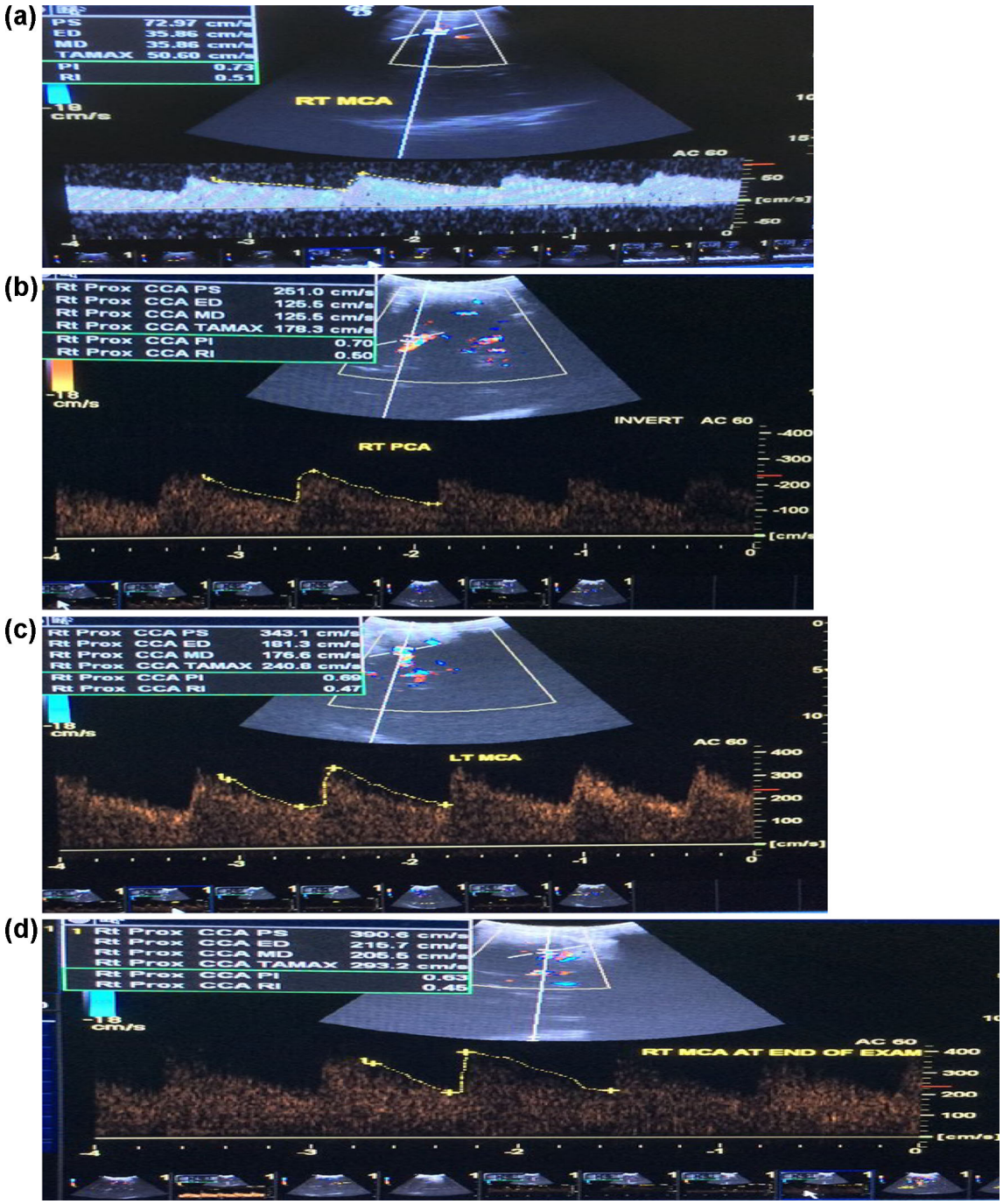

Fig. 1 TCD demonstrate time-averaged mean velocity **a** normal right MCA in hydroxyurea group. **b** Conditional right PCA in transfusion group. **c** Abnormal left MCA in transfusion group (TAMV 240.8 cm/s). **d** Abnormal right MCA in transfusion group (TAMV293.2 cm/s)

an abnormal TAMV $>$ 200 cm/s (TAMV of 293.2 cm/s and 240.8 cm/s), but clinically they remained stable. This was in agreement with [11].

In the view of these facts, cerebral arterial flow velocities obtained by TCD were lower in HU-treated SCA patients than in transfusion patients. It is possible that, a lower Doppler velocity in HU group due higher level of Hb, Hb F and decreased HbS. Hence, in hydroxyurea treated patients a different Doppler velocity range for stroke could be obtained. Further studies are needed in large sample size with long follow up, to see whether doppler limits needs to be recalibrated for such risk in HU treated patients with Sickle cell anaemia for better inference and to increase the power of the study. Our personal

Table 4 Correlation of TCD velocities and hematological parameters in SCA patients

Variables	Transfusion (n = 20)		Hydroxyurea (n = 20)	
	Correlation coefficient (r)	*P* value	Correlation coefficient (r)	*P* value
Hb level	0.049	0.837	0.054	0.820
Hct %	−0.211	0.372	−0.818	0.000
Hb F %	0.061	0.797	−0.039	0.872
WBC count	−0.311	0.181	0.102	0.669
Platelet count	−0.285	0.223	0.236	0.317

Spearman correlation was used

opinion that HU therapy and TCD screening represents a major step to prevent stroke.

Author Contributions SMM and AFT designed the study, analyzed the data and wrote the manuscript. HAH and SMM collected data, AFT revised the paper and approved the final version. MAS and SMM helped design the study, drafted and revised the manuscript and approved the final version.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interests.

Ethical Approval Patients were invited to participate in the study after getting informed consent and the steps and aim of the research were explained to participants The authors assert that all procedures performed in this study were in accordance with the ethical standards of the institutional committee of medical ethics and with the 1964 Helsinki declaration.

Informed Consent Informed consent was obtained from all individual participants included in the study. Research involving human participants.

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