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Hydroxyurea and Cardiac Sequelae in Children with Sickle Cell Disease

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Cardiac complications in sickle cell disease patients are widely expected. They may be related to iron deposition, anaemia or vasculitis. Hydroxyurea is a known drug that decreases haemoglobin (Hb) S levels. The objective of the study was to assess the effect of hydroxyurea on cardiac sequelae in children with sickle cell disease. Sixty-five sickle cell disease children were enrolled in the study; 37 of them were on regular follow up and hydroxurea treatment, whereas 28 were not. All patients underwent echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP) assay. Plasma levels of NTproBNP were significantly lower in sickle cell patients who were on hydroxyurea treatment than in those without this therapy (p=0.03). NTproBNP levels showed significant correlations with Hb (r=-0.72, p<0.05) and HbS levels (r=0.54, p<0.05). Significant positive correlations were detected between NTproBNP and echocardiography findings (r=0.64, p<0.01) including left ventricular mass index (r=0.78, p<0.01). In conclusion, hydroxyurea may reduce cardiac complications in children with sickle cell disease.

Key words: HYDROXYUREA; HEART; CHILDREN; ANEMIA, SICKLE CELL

INTRODUCTION

Sickle cell disease (SCD) is a common inherited haemoglobin (Hb) disorder that causes high morbidity in children (1). Cardiac complications in children with more severe SCD are a common problem (2). Pulmonary hypertension is considered one of the common risk factors in patients with SCD (3). SCD children with only HbS are more prone to vaso-occlusive attacks and other complications. Children who have higher levels of HbF may run less severe course (4, 5). SCD associated pulmonary hypertension was classified as group 1 with a subcategory of associated pulmonary hypertension at the 4th world congress (6).

N-terminal fragment of B-type natriuretic peptide (NTproBNP) is the inactive byproduct of pro-BNP cleavage. It is produced mainly in the left ventricle myocardium and to a less extent in other cardiac chambers (7, 8). Many studies indicated that NTproBNP levels had good correlations with pulmonary hypertension and diastolic dysfunctions (9, 10).

Hydroxyurea is a myelosuppressive agent that is considered the only effective drug proven to reduce the frequency of painful episodes. It raises the levels of HbF and Hb (11). This study was designed to assess the effect of hydroxurea on cardiac sequelae in children with SCD.

PATIENTS AND METHODS

We performed a prospective study at Haematology Unit and Outpatient Clinic of the Maternity and Children's Hospital, Abha, Saudi Arabia, between February 2016 and April 2017. All procedures performed in our study were in accordance with ethical standards of the Maternity and Children's Hospital Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Hospital Ethics Committee (REC23/16). A written informed consent was obtained from the parents before the study.

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Study design

Children with confirmed homozygous SCD, by clinical status, complete blood cell count, and haemoglobin electrophoresis were enrolled in this study. Patients who had suffered events such as pneumonia, heart failure, painful crises, vascular accidents, renal or hepatic impairment in the last six months before the study, congenital heart disease, diabetes mellitus, hypothyroidism and haemoglobinopathies other than SCD were excluded.

A total of 65 children with SCD were enrolled in the study. They were divided into two groups, i.e. group 1 with 37 patients (mean age 10±2.3 years) that were on regular hydroxyurea treatment with a dose of 20-35 mg/kg/day for at least one year and group 2 with 28 patients (mean age 9±3.4 years) that were not treated with hydroxyurea. Group 2 patients were not on regular follow up or were referred for the first time to our hospital. All patients underwent thorough medical history taking and complete examination, NTproBNP assessment, and echocardiography (ECG) evaluation.

Plasma NT-proBNP assay

Plasma NT-proBNP was assessed by using a solid double antibody sandwich technique with chemiluminescence immunoassay (Immulite 2500, Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Echocardiography evaluation

It was performed using a Vivid 5 echo machine, Alkan Company 2014 version with a 3-MHz probe including M-mode, 2 D Doppler and colour Doppler. All patients were assessed by the same paediatric cardiologist and measurements were calculated by the same machine and the same software. Tricuspid regurgitant jet velocity more than 2.5 m/second (pressure gradient more than 25 mm Hg) indicated pulmonary hypertension in the absence of right ventricular outflow obstruction. All cardiac dimensions and pressure gradient were studied over three cycles. Left ventricular mass index (LVMI) was calculated using Devereux formula:

$$LVMI\ (g)=0.8\{1.04[(IVS+LVDD+LVPW)^3-3LVDD]\}+0.6\ (12).$$

Data were compared to the corresponding normal values for age and sex. ECG was recorded at the same time.

Statistical analysis

Numerical data were expressed as mean ± standard deviation. Student's t-test or Mann-Whitney test was used to compare numerical variables between the groups. Categorical variables were analysed using χ^2 distribution or Fisher exact test. Spearman's correlation test was used to determine possible correlations between different study parameters. The level of statistical significance was defined by $p<0.05$. Statistical analysis was performed by using the SPSS version 22 (SPSS, Chicago, IL, USA) software.

RESULTS

A total of 65 children with SCD were enrolled in this study. Patients were divided into two groups according to regular use of hydroxyurea: group 1 on regular treatment with hydroxyurea) and group 2 with no hydroxyurea therapy. Their

TABLE 1. **Descriptive clinical and laboratory characteristics of children with sickle cell disease**

Characteristic	Group 1 (n=37)	Group 2 (n=28)	p value
Sex Male (%)[a] Female (%)[a]	(21/16) 21 (57) 16 (43)	(15/13) 15 (54) 13 (46)	0.59
Age (years)[b]	11.5±3.2	12.1±1.2	0.21
Haemoglobin (gm/dL)[b]	8.57±1.0	7.1±1.2	**0.01**
HbS level (gm/dL)[b]	6.7±1.7	7.2± 2.1	0.06
HbF level (gm/dL)[b]	3.4±2.2	1.9±0.8	**0.02**
Total bilirubin (mg/dL)[b]	2.02±1.31	3.31±1.4	**0.04**
Direct bilirubin (mg/dL)[b]	0.4±0.3	0.49±0.42	0.06
Ferritin (ng/mL)[b]	570.43±964.32	761.12±1021	0.18
NTproBNP (pg/mL)[b]	84.20±16.5	112.59±20.2	**0.001**

[a]Number (%); [b]values are means ± SD.

TABLE 2. **Echocardiographic findings in study groups**

Finding	Group 1 (n=37)	Group 2 (n=28)	p value
SPAP[a]	16.5±8.3 mm Hg	29.5±11.4 mm Hg	**0.02***
EF (%)[a]	63.4±22.6	60.9±28.4	0.3
FS (%)[a]	41.4±13.6	37.1±15.3	0.4
LVMI[a]	31.1±5.6	39.7±8.1	**0.04***
Right ventricular diastolic dimension[a]	14.3±4.5	15.2±5.1	0.3

[a]values are means ± SD; *p value significant; SPAP = systolic pulmonary artery pressure; EF = ejection fraction; FS = fractional shortening; LVMI = left ventricular mass index

TABLE 3. **Correlations between NTproBNP and different parameters in diseased children**

Parameter for correlation	Haemoglobin	Haemoglobin S	SPAP	LVMI
NTproBNP	r=-0.72* p<0.05	r=0.54* p<0.05	r=0.64* p<0.01	r=0.78* p<0.01

*significant correlation; SPAP = systolic pulmonary artery pressure; LVMI = left ventricular mass index

clinical and laboratory characteristics are shown in Table 1. As shown in Table 1, there was no significant between-group difference according to sex distribution, age, HbS, direct bilirubin and serum ferritin. Hb, HbF and total bilirubin levels were significantly higher in group 1 in comparison to group 2 ($p<0.03$, $p<0.02$ and $p<0.04$, respectively), whereas NTproBNP was significantly lower in group 1 in comparison to group 2 ($p<0.03$).

Systolic pulmonary artery pressure (SPAP) and LVMI were significantly lower in group 1 than in group 2 patients ($p=0.02$ and $p=0.04$, respectively). The ECG findings in the study groups are shown in Table 2.

Our results demonstrated a significant negative correlation between NTproBNP levels and Hb level ($r=-0.72$, $p<0.05$) and significant positive correlations between NTproBNP level and HbS levels ($r=0.54$, $p<0.05$). Significant positive correlations were detected between NTproBNP and ECG findings including SPAP ($r=0.64$, $p<0.01$) and LVMI ($r=0.78$, $p<0.01$), as shown in Table 3.

DISCUSSION

As a multisystem disorder, SCD may affect many organs including the heart. Cardiac involvement may be presented in many features with different pathologies (13). Hydroxyurea seems to control the incidence of acute vaso-occlusive attacks and its complications and improves exercise tolerance (11, 14). Results of our study showed that both total Hb and HbF levels were significantly higher in group 1 patients who regularly received hydroxyurea while total bilirubin and serum ferritin were significantly lower than in group 2, which was consistent with the studies evaluating effectiveness of the use of hydroxyurea in SCD patients (15, 16). NTproBNP levels were statistically significantly lower in treated patients. Shinichi *et al*. recorded positive correlation between NTproBNP and severity of anaemia in SCD children (17). Higher levels of NTproBNP indicate greater volume and pressure overload on cardiac chambers (18). Many studies showed that elevated cardiac output was commonly associated with SCD (19, 20). Cardiac output in chronic anaemic patients may be elevated as a consequence of the renin-angiotensin-aldosterone system activation and sympathetic hyperactivity, and this myocardium overload may lead to increased NTproBNP release (21, 22). Chronic severe anaemia induces myocardial ischemia on top of persistent hypoxia, which may cause vasodilatation with low systemic vascular resistance mediated by endothelial nitric oxide (23). Group 2 patients showed significantly higher SPAP and LVMI than those group 2 patients, which reflected less cardiac involvement in the patients regularly treated with hydroxyurea. These results regarding the non treated group are in agreement with the studies by *Kato et al*. and *Pankanker et al*. (24, 25) that report elevated SPAP in patients with progressive SCD. The same results were noticed by *Shinichi et al*. (17). Other mechanisms may be involved in cardiac affection in SCD patients including iron overload, myocardial ischemia mediated through hypoxia, anaemia and rarely red blood cell sickling (18). Our results showed that LVMI was significantly elevated in the non treated group. According to Devereux formula, LVMI elevation reflects the increment of interventricular septum, left ventricular posterior wall and left ventricular dimension in diastole (12). These parameters are affected by many factors in SCD patients including Hg and HgS levels. In previous studies, there was significant correlation between HbS levels and left ventricular hypertrophy (26, 27). Our hydroxyurea treated patients showed higher Hb levels and lower LVMI. These findings are in agreement with many previous studies (27, 28). Accordingly, regular use of hydroxyurea is considered a prophylactic treatment against left ventricular hypertrophy.

The benefits recorded for the use of hydroxyurea in SCD patients include its efficacy in reducing multiorgan damage manifestations in children including hypoxemia, pulmonary hypertension, proteinuria and glomerular injury, which may lead to decrement of myocardial load (15). The present study showed significant positive correlations of NTproBNP and echocardiographic SPAP and LVMI. Many studies in SCD patients suggest that NTproBNP is a good predictor of tricuspid regurgitation and elevated pulmonary pressure (8, 10, 29). Other studies have reported elevated serum NTproBNP levels in disease progression and development of heart failure, and suggest that NTproBNP may be of prognostic value for left ventricular diastolic dysfunction These findings indicate that poor control of SCD children may lead to pulmonary hypertension and development of impaired diastolic functions, indicating the benefit of using hydroxyurea to decrease these sequelae (17, 30, 31).

Our study limitation was the small cohort of patients, which was not sufficient to enable us to give firm statement about the use of hydroxyurea. Additional studies are necessary.

CONCLUSION

The current study suggested that patients with SCD are at a risk of cardiac involvement and regular hydroxyurea treatment may reduce this risk.

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SAŽETAK

Hidroksiureja i srčane posljedice u djece s bolešću srpastih stanica

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Srčane komplikacije su vrlo vjerojatne u bolesnika s bolešću srpastih stanica, a mogu biti povezane s odlaganjem željeza, anemijom ili vaskulitisom. Hidroksiureja je lijek koji snižava razine hemoglobina (Hb) S. Cilj istraživanja bio je procijeniti učinak hidroksiureje na srčane posljedice u djece s bolešću srpastih stanica. U studiju je bilo uključeno 65 djece s bolešću srpastih stanica, od kojih je 37 bilo na terapiji hidroksiurejom uz redovito praćenje, a preostalih 28 nije primalo ovu terapiju. U svih bolesnika učinjena je ehokardiografija i test NT-proBNP. Razine NT-proBNP u plazmi bile su značajno niže u bolesnika s bolešću srpastih stanica koji su primali terapiju hidroksiurejom nego u onih bez ove terapije (p=0,03). Razine NT-proBNP pokazale su značajnu korelaciju s razinama Hb (r=-0,72, p<0,05) i HbS (r=0,54, p<0,05). Značajna pozitivna korelacija utvrđena je između NT-proBNP i ehokardiografskih nalaza (r=0,64, p<0,01) uključujući indeks mase lijeve klijetke (r=0,78, p<0,01). Zaključno, hidroksiureja može smanjiti srčane komplikacije kod djece s bolešću srpastih stanica.

Ključne riječi: HIDROKSIUREJA; SRCE; DJECA; ANEMIJA, BOLEST SRPASTIH STANICA