

Increased sexual performance of sickle cell patients with hydroxyurea

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Abstract

Background: There is a fear of infertility caused by hydroxyurea with unknown reasons in some regions of Turkey. We tried to understand effects of hydroxyurea on sexual performance in Sickle Cell Diseases (SCDs).

Methods: The study was performed between March 2007 and September 2013.

Results: The study included 337 patients (169 females). Mean number of painful crises per year was decreased with hydroxyurea (10.3 versus 1.7 crises per year, $p < 0.000$). Mean severity of painful crises was decreased, too (7.8/10 versus 2.2/10, $p < 0.001$). Although mean body weight, hematocrit (Hct) value, and mean corpuscular volume (MCV) increased, white blood cell (WBC) and platelet (PLT) counts and direct bilirubin, total bilirubin, and lactate dehydrogenase (LDH) values of serum decreased ($p < 0.000$ for all). Parallel to these improvements, the mean number of sexual intercourse per month increased, significantly (2.0 versus 6.8, $p < 0.001$). We detected hepatotoxicity in 13 acute painful crises among 1.211 episodes, totally (1.0%). All of them healed completely with withdrawal of all of the medications but not hydroxyurea alone. The solitary adverse effect of hydroxyurea was prominent

anemia in higher dosages in 16 patients (4.7%), and they completely healed with transient withdrawal and decreased dosages thereafter.

Conclusion: Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, direct and total bilirubin, and LDH values of serum, whereas it increases mean body weight, Hct value, and MCV. Parallel to these physical and clinical improvements, mean number of sexual intercourse per month and chance of fertility increased in both genders in hydroxyurea users.

Key words: Hydroxyurea, sickle cell diseases, sexual performance, chronic endothelial damage, metabolic syndrome

Introduction

Probably aging is the major physical health problem of the human being, and systemic atherosclerosis may be the major underlying cause. Systemic atherosclerosis is an irreversible process mainly keeping afferent vasculature due to the much higher blood pressure (BP) in them. Accelerating factors of atherosclerosis are collected under the heading of metabolic syndrome in the literature including physical inactivity, smoking, alcohol, chronic inflammation and infections, cancers, excess weight, dyslipidemia, elevated BP, and insulin resistance for the development of irreversible diseases including obesity, hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheral artery disease, and stroke (1-6). Early aging and premature death are the terminal end points of the syndrome. Similarly, sickle cell diseases (SCDs) are accelerated atherosclerotic processes that are characterized by sickle-shaped red blood cells (RBCs) caused by homozygous inheritance of the hemoglobin S (Hb S) (7, 8). Glutamic acid is replaced with a less polar amino acid, valine, in the sixth position of the beta chain of the Hb S. Presence of valine promotes polymerisation of the Hb S. So Hb S causes RBCs to change their normal elastic and biconcave disc shaped structures to hard bodies. The decreased elasticity instead of shapes of RBCs may be the main pathology of the diseases. The normally present sickling process in whole life span is exaggerated with various stresses of the body. The RBCs can take their normal elastic shapes after normalization of these stresses, but after repeated cycles of sickling and unsickling, they become permanent hard bodies. The hard bodies induced chronic endothelial damage together with tissue ischemia and infarctions are the terminal consequences, so life expectancy of such patients is decreased by 25 to 30 years (9). We tried to understand effects of hydroxyurea on sexual performance in the SCDs.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and September 2013. All patients with the SCDs were included into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. Their medical histories including smoking habit, regular alcohol consumption, and leg ulcers were learnt. Frequency of painful crises was detected as a mean number of crises per year, and severity of them as a mean degree between 0 to 10 according to patient's self-explanation. Mean number of sexual intercourse per month was learnt. Cases with a history of three pack-year were accepted as smokers, and cases with a history of one drink a day for three years were accepted as drinkers. A check up procedure including body weight, serum creatinine value, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiography, a Doppler echocardiography, an

abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging of hips was performed. Other bone areas for avascular necrosis were scanned according to the patients' complaints. Cases with acute painful crisis or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic BP of pulmonary artery, and renal and hepatic function tests were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (10). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension (11). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females on the silent phase. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, ultrasonographic evaluation, and liver biopsy in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0 and with the presence of Schamroth's sign (12, 13). A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Then, a hydroxyurea therapy was initiated to all patients with an initial dose of 15 mg/kg/day, and then the dose was increased up to the final dose of 35 mg/kg/day according to patients' requirements and compliances. Finally, the mean number of painful crises per year, mean severity of painful crises, mean number of sexual intercourse per month, mean body weight, white blood cell (WBC) and platelet (PLT) counts, hematocrit (Hct) value, mean corpuscular volume (MCV), and the direct bilirubin, total bilirubin, and lactate dehydrogenase (LDH) values of serum were compared before and after the hydroxyurea therapy. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 337 patients with the SCDs (169 females and 168 males). Their mean ages were 28.4 ± 9.3 (8-59) versus 29.8 ± 9.3 (6-58) years in females and males, respectively ($p > 0.05$). The final dose of 35 mg/kg/day hydroxyurea therapy was just achieved in 25 cases (7.4%), and the usual dose was 500 mg twice daily during the 7-year follow-up period. During the period, the mean number of painful crises per year was decreased with the treatment, significantly (10.3 versus 1.7 crises per year, $p < 0.000$). The mean severity of painful crises was decreased, too (7.8/10 versus 2.2/10, $p < 0.001$). Although the mean body weight, mean Hct value, and MCV increased, the WBC and PLT counts and the direct bilirubin, total bilirubin, and LDH values of serum decreased with the therapy, significantly ($p < 0.000$ for all) (Table 1).

Table 1: Characteristic features of sickle cell patients before and after hydroxyurea therapy

Variables	Before hydroxyurea therapy	p-value	After hydroxyurea therapy
Mean number of painful crises per year	10.3 ± 10.6 (0-48)	<0.000	1.7 ± 1.1 (0-6)
Mean severity of painful crises	7.8 ± 2.2 (0-10)	<0.000	2.2 ± 1.7 (0-10)
Body weight (kg)	59.1 ± 11.4 (37-95)	<0.000	65.2 ± 13.0 (46-107)
White blood cell (μL)	15.050 ± 6.148 (4,890-38,800)	<0.000	11.349 ± 5.029 (5,010-31,850)
Hematocrit value (%)	23.2 ± 4.0 (16-35)	<0.000	27.8 ± 3.4 (20-36)
Mean corpuscular volume (fL)	88.7 ± 9.6 (57-112)	<0.000	105.2 ± 13.6 (66-129)
Platelet (μL)	449,840 ± 217,370 (169,000-1,561,000)	<0.000	430,840 ± 142,681 (219,000-936,000)
Total bilirubin (mg/dL)	5.3 ± 5.6 (0.6-38.2)	<0.000	3.1 ± 2.2 (0.7-11.0)
Direct bilirubin (mg/dL)	2.0 ± 3.4 (0.2-15.0)	<0.000	0.9 ± 0.9 (0.2-6.0)
Lactate dehydrogenase (IU/L)	647.5 ± 265.8 (196-1,552)	<0.000	509.9 ± 315.4 (235-2,218)

Table 2: Sickle cell patients with associated disorders

Variables	Prevalence
Autosplenectomy	46.8%
Avascular necrosis of bones	18.9%
Leg ulcers	12.7%
Pulmonary hypertension	11.5%
Chronic renal disease	8.3%
Coronary heart disease	7.7%
Digital clubbing	6.5%
Stroke	6.5%
Exitus	5.3%
Chronic obstructive pulmonary disease	4.7%
Cirrhosis	3.2%

Parallel to these physical and clinical improvements, the mean number of sexual intercourse per month increased from 2.0 ± 1.3 (0-7) before the therapy to 6.8 ± 2.4 (0-13) after the therapy ($p < 0.001$). During the 7-year follow-up period, we detected hepatotoxicity just in 13 acute painful crises among 1,211 episodes, totally (1.0%). Interestingly, two of the patients were females with a mean age of 38.5 years and 11 cases were males with a mean age of 32.3 years. So the hepatotoxicity during acute painful crises was significantly higher in males (6.5% versus 1.1%, $p < 0.001$). All of the cases healed completely with withdrawal of all of the medications but not hydroxyurea alone. The solitary adverse effect of hydroxyurea therapy was bone marrow suppression with prominent anemia in higher dosages during the 7-year follow-up period. It was seen in seven females (4.1%) with a mean age of 36.5 years and nine males with a mean age of 28.0 years (5.3%, $p > 0.05$), and they completely healed with transient withdrawal and decreased dosages of hydroxyurea thereafter. Just in a male patient with an age of 22 years, we needed to support with two units of RBCs suspensions due to the symptomatic palpitation. None of the patients needed any supportive therapy for thrombocytopenia or leukopenia. Although the presence of prominent anemia, none of the patients were on acute painful crisis during the detection. On the other hand, we detected autosplenectomy in 46.8%, avascular necrosis of bones in 18.9% (90.6% at the hip joints), leg ulcers in 12.7%, pulmonary hypertension in 11.5%, CRD in 8.3%, CHD in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, COPD in 4.7%, and cirrhosis in 3.2% of the patients (Table 2). Although smoking was observed in 6.5% (22) of the patients, there was only one case (0.2%) of regular alcohol consumption, who was not cirrhotic at the moment. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both. Prevalence of mortality was similar in both genders (4.7% versus 5.9% in females and males, respectively, $p > 0.05$), and mean ages of such cases were 32.1 versus 29.1 years in females and males, respectively ($p > 0.05$).

Discussion

SCDs particularly affect microvascular endothelial cells of the body (14, 15), since the capillaries are the main distributors of the hard bodies into the tissues. Because of the microvascular nature of the diseases, we can observe healing of leg ulcers with hydroxyurea therapy in early years of life, but later in life the healing process is difficult due to the excessive fibrosis around the capillaries. Eventually, the mean survival was around 42 years in males and 48 years in females in the literature (9), whereas it was 29.1 and 32.1 years, respectively, in the present study ($p > 0.05$). The great differences between the survival may be secondary to the delayed initiation of hydroxyurea therapy by the medical doctors and a fear of infertility caused by hydroxyurea in the SCDs patients with unknown reasons in Antakya region of Turkey. On the other hand, the relatively longer survival of females with the SCDs should also be researched, effectively. As a result of such a great variety of clinical presentation, it

is not surprising to see that the mean body weight and body mass index (BMI) were significantly retarded in the SCDs patients (16). Probably parallel to the lower mean body weight and BMI, mean values of the low density lipoprotein cholesterol, alanine aminotransferase, and systolic and diastolic BPs were also lower in the SCDs (16), which can be explained by definition of the metabolic syndrome (17, 18).

Painful crises are the most disabling signs of the SCDs, and infections may be the most frequent triggering factors of them. Inflammation, operations, depression, and other stressful conditions of the body may also trigger them. Although some authors reported that the painful crises themselves may not be life threatening (19), increased metabolic rate during the painful crises may terminate with an increased risk of mortality mainly due to underlying end-organ insufficiency. Probably pain is the result of a generalized inflammatory process on the vascular endothelium, and the increased WBC and PLT counts and the decreased Hct values show presence of a chronic inflammation during their whole lives in such patients (20). For example, leukocytosis even in the absence of an infection was an independent predictor of the severity (21), and it was associated with an increased risk of stroke probably by releasing cytotoxic enzymes and causing endothelial damage in another study (22). Due to the severity of pain, narcotic analgesics are usually required to control them (23), but according to our experiences, simple and repeated RBC transfusions are highly effective during the severe crises both to relieve pain and to prevent sudden deaths which may develop secondary to the end-organ insufficiencies on chronic inflammatory background of the SCDs (24).

Hydroxyurea is an effective therapeutic option for the treatment of chronic myeloproliferative disorders and SCDs. It interferes with cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F) (25, 26), its main action may be the suppression of leukocytosis and thrombocytosis via blocking the DNA synthesis in the SCDs. By this way, the chronic inflammatory process of the SCDs that initiated at birth on the vascular endothelium is suppressed to some extent. Due to the same action, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in viral hepatitis cases, although presence of continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own immune systems, particularly by the actions of WBCs and PLTs. So suppression of excessive proliferation of WBCs and PLTs probably limits the endothelial damage-induced tissue ischemia and infarctions all over the body. Similarly, it was reported that the lower neutrophil counts were associated with lower crisis rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain

and extent of tissue damage (27). On the other hand, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels, significantly (27).

Physicians at the National Institutes of Health Consensus Conference agreed that hydroxyurea is underused both in children and adults due to some reasons. Hydroxyurea is a chemotherapeutic agent, thus it is not used by women planning to become pregnant in the near future. Additionally, there is fear of potentially increased risk of cancers in people (28). However, the cancer risk has not been substantiated by more than a decade of using hydroxyurea for adults (29). Although investigational and post-marketing data show risk to fetus (30), potential benefits may outweigh potential risks in pregnancy. On the other hand, there is a fear of infertility caused by hydroxyurea with unknown reasons in Antakya region of Turkey. According to our experiences, there are several SCDs' patients with delayed menarche, early menopause, abortus, stillbirth, loss of libido, erectile dysfunctions, priapism, and an eventual infertility. Moderate anemia caused by SCDs themselves, chronic disease anemia, vitamin B12 and folic acid deficiencies, chronic vascular endothelial inflammation all over the body, end-organ insufficiencies, movement disorders due to the leg ulcers and avascular necrosis of bones, painful crises, frequent hospitalizations, invasive procedures, repeated blood transfusions and medications, anorexia, cachexia, relative immune suppression, frequent infections and major depressions may be found among several underlying causes of them in the SCDs' patients. The decreased number and severity of painful crises, increased mean body weight, decreased WBC and PLT counts, and increased Hct value with hydroxyurea therapy will probably result with resolution of most of the above problems to some extent. As a result, the mean number of sexual intercourse per month increases, significantly. So hydroxyurea does not cause infertility instead it increases chance of fertility in both genders with several pathways. It is clear that there is a need for more effective treatment regimens in the SCDs, but until they become available, hydroxyurea must be used in all cases, and its dosage has to be increased as much as possible until the normalization of all symptoms, signs, and laboratory abnormalities.

Hydroxyurea probably has a life-saving role in the SCDs. The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with sickle cell anemia (Hb SS) and compared the results of patients treated with hydroxyurea or placebo (31). The study particularly researched effects of hydroxyurea on painful crises, acute chest syndrome, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (31). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (31). But this study was performed just in severe Hb SS cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (31). Whereas in our study, we used all subtypes of the

SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p < 0.000$) with an additional decreased severity (7.8/10 versus 2.2/10, $p < 0.000$). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (32). The underlying disease severity remains critical to determine prognosis, but hydroxyurea may decrease severity of disease and prolong survival (32). Probably the chronic endothelial damage of the SCDs is initiated at birth, and complications may start to be seen even in infancy. For example, infants with lower hemoglobin levels were more likely to have a higher incidence of clinical events such as acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidence of them (33). Hydroxyurea therapy in early years of life may also protect splenic function, improve growth, and prevent end-organ insufficiencies by decreasing early capillary endothelial damage. Transfusion programmes can also reduce all of the complications of the SCDs, however transfusions carry many potential risks including infection transmission, development of allo-antibodies making subsequent transfusions difficult, and iron overload.

As a conclusion, hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, direct and total bilirubin, and LDH values of serum, whereas it increases mean body weight, Hct value, and MCV. Parallel to these physical and clinical improvements, the mean number of sexual intercourse per month and chance of fertility increases in both genders in hydroxyurea users.

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