Preoperative management of sickle cell patients with hydroxyurea

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Abstract

Background: We tried to understand whether or not there are some beneficial changes of health parameters with hydroxyurea in sickle cell diseases (SCDs) cases.

Methods: All SCDs cases were enrolled, and a hydroxyurea therapy was initiated.

Results: We studied 337 patients, totally. Hydroxyurea was well-tolerated with a majority of patients (80.1%). Mean number (10.3 versus 1.7 crises per year, p<0.000) and mean severity of painful crises decreased, significantly (7.8 versus 2.2, p<0.001). Although body weight and mean hematocrit (Hct) value increased, white blood cell (WBC) and platelet (PLT) counts and total and direct bilirubin and lactate dehydrogenase (LDH) levels decreased, significantly (p<0.000 for all). On the other hand, there were avascular necrosis of bones in 18.9%, leg ulcers in 12.7%, pulmonary hypertension in 11.5%, chronic renal disease in 8.3%, coronary heart disease in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, chronic obstructive pulmonary disease in 4.7%, and cirrhosis in 3.2% of the patients.

Conclusion: SCDs are chronic inflammatory disorders initiating at birth. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, and it increases body weight and Hct value, all of which indicate a decreased inflammatory process in patients. Thus elective surgical procedures should be performed after a few months of treatment with hydroxyurea in non-users. By this way, beside decreased requirement of blood transfusions, perioperative morbidity and mortality will also be lowered due to decreased inflammatory process on capillary endothelium all over the body.

Key words: Sickle cell diseases, chronic endothelial inflammation, hydroxyurea

Introduction

Systemic atherosclerosis may be the major underlying cause of aging in human beings and even in animals. It is an irreversible process initiating at birth. Although it keeps to mainly the larger, high blood pressure (BP) carrying vessels, all arteries, arterioles, and even capillaries are affected with some extent. Some of the accelerating factors of the systemic process are overweight, dyslipidemia, elevated BP, and insulin resistance for the development of terminal diseases such as obesity, hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheric artery disease, and stroke, all of which are collected under the heading of metabolic syndrome (1-6). On the other hand, sickle cell diseases (SCDs) are systemic microangiopathic processes that are caused by homozygous inheritance of hemoglobin S (Hb S) (7,8). Glutamic acid is replaced with 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 red blood cells (RBCs) to change their normal elastic and biconcave disc shaped structures to hard bodies. The decreased elasticity of RBCs instead of their shapes may be the central pathology of the diseases. The sickling process is present in whole life, but is exaggerated during stressful conditions due to the increased basal metabolic rate. The RBCs can take their normal elastic structures after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they become hard bodies, permanently. The hard cells induced chronic endothelial damage and infarcts at the microvascular level, even in the absence of obvious vascular occlusions due to the edematous endothelium, are the terminal consequences of the diseases, so life expectancy is decreased up to 30 years (9). We tried to understand whether or not there are some beneficial changes of health parameters with hydroxyurea therapy in the SCDs.

Material and Methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and October 2013. All patients with SCDs were enrolled 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. 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 on three occasions, 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 permanently elevated serum creatinine level of 1.3 mg/dL or higher on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, 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' requirement and compliance. Finally, the mean number and severity of painful crises, body weight, white blood cell (WBC) and platelet (PLT) counts, hematocrit (Hct) value, mean corpuscular volume (MCV), and the total and direct bilirubin and lactate dehydrogenase (LDH) levels of the 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). The mean ages of them were 28.4 ± 9.3 (8-59) versus 29.8 ± 9.3 (6-58) years in females and males, respectively ($p>0.05$). The hydroxyurea treatment was used and well-tolerated with a high majority of cases (80.1%), and the remaining cases could not be followed up. We have not observed any major side effect of the therapy during the follow-up period. The final dose of 35 mg/kg/day was required just 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 significantly decreased with the treatment (10.3 versus 1.7 crises per year, $p<0.000$). The mean severity of painful crises was decreased, too (7.8 versus 2.2, $p<0.001$). Although the body weight, mean Hct value, and MCV increased, the WBC and PLT counts and the total and direct bilirubin and LDH levels of the serum decreased with the therapy, significantly ($p<0.000$ for all) (Table 1). On the other hand, we detected autosplenectomy in 46.8%, avascular necrosis of bones in 18.9% (90.6% at hips, 10.9% at shoulders, 9.3% at knees, 6.2% at elbows,

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)
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% (158)
Avascular necrosis of bones	18.9% (64) (90.6% at the hips)
Leg ulcers	12.7% (43)
Pulmonary hypertension	11.5% (39)
Chronic renal disease	8.3% (28)
Coronary heart disease	7.7% (26)
Digital clubbing	6.5% (22)
Stroke	6.5% (22)
Exitus	5.3% (18)
Chronic obstructive pulmonary disease	4.7% (16)
Cirrhosis	3.2% (11)

3.1% at ankles, and 1.5% at wrists), 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 time. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both. Prevalences of mortality were 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 mainly affect microvascular endothelium of the body (14), because the capillary system is the main distributor of the hard bodies to tissues, so it is destroyed much more severely than the larger vessels. Because of the microvascular nature of the diseases, we can observe healing of leg ulcers with hydroxyurea therapy in early years of life, but the healing process is difficult due to the

excessive fibrosis around the capillaries later in life. Eventually, the mean survival was 42 years in males and 48 years in females in the literature (9), whereas it was 29 and 32 years, respectively, in the present study ($p>0.05$). According to our experiences, the great differences between the survival are secondary to the initiation of hydroxyurea treatment in early years of life, even at birth in developed countries. On the other hand, the prolonged survival of females with SCDs and the longer overall survival of females in the world (15) could not be explained by well known strong atherosclerotic effects of smoking alone; instead it may be explained by the dominant role of male sex in life (16). As a result of such a great variety of clinical presentations, it is not surprising to see that the mean body weight and body mass index (BMI) were retarded in the SCDs cases (17). Parallel to the lower body weight and BMI, the low density lipoprotein cholesterol, alanine aminotransferase, and systolic and diastolic BPs were also lower in the SCDs (17), which can be explained by definition of the metabolic syndrome (18,19).

Painful crises are the pathognomonic symptoms of the SCDs. Although painful crises themselves may not be life threatening directly (20), increased basal metabolic rate with any underlying cause such as infection, tissue damage, operation, or depression usually terminate with crises, so multiorgan failures on the chronic inflammatory background of the SCDs are not rare in such circumstances (21,22). Probably pain is due to the disseminated inflammatory process of the capillary endothelium, and the increased WBC and PLT counts and decreased Hct values indicate presence of a chronic inflammatory process during their whole lives in such patients. Increased WBC counts even in the absence of an infection, tissue damage, operation, or depression was an independent predictor of the disease severity (23), and it was associated with an increased risk of stroke, probably by releasing cytotoxic enzymes and causing endothelial damage in the brain (24). Due to the severity of pain, narcotic analgesics are usually required to control them (25), but according to our practice, simple RBC transfusions are highly effective during the severe crises, both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on the prolonged inflammatory background of the SCDs.

Hydroxyurea is an effective drug in several chronic myeloproliferative disorders and SCDs. It interferes with cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are building blocks of DNA. Hydroxyurea mainly acts on hyperproliferative cells. Although the action of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (Hb F) (26,27), its main action is probably suppression of leukocytosis and thrombocytosis in the SCDs. By this way, the continuous inflammatory process of the SCDs that initiated at birth on the capillary endothelium is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferative skin cells. As in viral hepatitis cases, although presence of a continuous damage of hard RBCs on the capillary endothelium in the SCDs, the severity of destructive process is probably exaggerated by the patients' immune system, especially by the actions of WBCs and PLTs (28). So suppression of excessive proliferation of WBCs and PLTs probably limits the capillary damage-induced tissue ischemia and infarctions all over the body. Similarly, it was reported that lower neutrophil counts were associated with lower crises rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and extent of tissue damage (29). On the other hand, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels, significantly (29).

Physicians at the National Institutes of Health Consensus Conference agreed that hydroxyurea is underused both in children and adults. First of all, due to the relatively younger mean ages of the SCDs patients, females and even males may not use the drug for a long period of time just to get a baby with some additional inhibitory effects of the chronic inflammatory disease on fertility. Additionally, there is fear of cancers in people, since hydroxyurea is a chemotherapeutic agent (30). However, the cancer risk has not been substantiated by more than a decade of using hydroxyurea for adults (31). Although some data show risk to fetus (32), potential benefits may outweigh potential risk even during pregnancy. According to our experiences, there are several female patients with infertility, abortus, and stillbirth in the absence of hydroxyurea therapy, and the decreased number and severity of painful crises, increased body weight, decreased WBC and PLT counts, and increased Hct value with the hydroxyurea therapy will probably result with resolution of the above problems to some extent. It is clear that there is a need for more effective treatment regimens in the SCDs, but until they become more available, hydroxyurea should be used in all cases, and its dose should be kept higher in the moderate and severe patients.

Hydroxyurea may have a critical role in the SCDs (14). 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 (33). The study especially searched effects of the drug on painful crises, acute chest syndrome, and need of RBC transfusions. The outcomes were so overwhelming in favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated to all patients. The patients treated with hydroxyurea had a 44% decrease of hospitalizations, and there was a strong and independent association of lower neutrophil counts with the lower crisis rates (33). 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 (33). Whereas in our study, we used 337 patients with all subtypes and clinical severity of SCDs, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8 versus 2.2, $p<0.000$). Parallel to the above results, adult SCDs patients using hydroxyurea appear to have reduced mortality rate after a 9-year follow-up period (34). Although the underlying disease severity remains critical to determine

prognosis, hydroxyurea may decrease severity of disease (34) and prolong survival (14). Probably chronic endothelial damage of the capillaries 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 higher incidences of acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidence of them (35). Hydroxyurea in early life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions by preventing early capillary damage. Transfusion programmes also reduce the complications, but they carry risks including transmission of infections, development of allo-antibodies causing subsequent transfusions difficult, and iron overload.

As a conclusion, the SCDs are chronic inflammatory disorders initiating at birth. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, and it increases body weight and Hct value, all of which indicate a decreased inflammatory process in the patients. Thus elective surgical procedures should be performed after a few months of treatment with hydroxyurea in non-users. By this way, beside decreased requirement of blood transfusions, perioperative morbidity and mortality will also be lowered due to decreased inflammatory process on capillary endothelium all over the body.

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