Red blood cell supports in severe clinical conditions in sickle cell diseases

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Abstract

Background: Sickle cell diseases (SCDs) are accelerated atherosclerotic processes. We tried to understand whether or not there is a prolonged survival with the increased number of red blood cells (RBC) transfusion in the SCDs.

Methods: As one of the significant endpoints of the SCDs, cases with chronic obstructive pulmonary disease (COPD) and without, were collected into the two groups.

Results: The study included 428 patients (221 males). There were 71 patients (16.5%) with COPD. Mean age was significantly higher in the COPD group (32.8 versus 29.8 years, P=0.005). Male ratio was significantly higher in the COPD group, too (78.8% versus 46.2%, P<0.001). Smoking (35.2% versus 11.4%, P<0.001) and alcohol (7.0% versus 1.9%, P<0.01) were also higher among the COPD cases. Beside these, priapism (14.0% versus 3.0%, P<0.001), HCV RNA positivity (2.7% versus 0.5%, P<0.05), cirrhosis (8.4% versus 3.3%, P<0.05), leg ulcers (23.9% versus 12.0%, P<0.01), digital clubbing (25.3% versus 6.7%, P<0.001), coronary heart disease (23.9% versus 13.7%, P<0.05), chronic renal disease (15.4% versus 7.0%, P<0.01), stroke (16.9% versus 8.1%, P<0.01), and mean transfused RBC units in their lives (63.8 versus 33.0, P=0.003) were all higher among the COPD cases. This was probably due to the higher number of transfused RBC units; the mean age of mortality was also higher in the COPD group, significantly (38.3 versus 30.4 years, P=0.04).

Conclusion: SCDs are chronic catastrophic processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures in early years of life. RBC supports in severe clinical conditions probably prolong survival of the patients.

Key words: Sickle cell diseases, chronic endothelial damage, red blood cell support

Introduction

Chronic endothelial damage may be the major cause of aging and mortality by inducing disseminated cellular hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are mainly involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, weight gain, smoking, and alcohol for the development of irreversible endpoints including obesity, hypertension, diabetes mellitus, cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, teeth loss, and stroke, all of which terminate with early aging and mortality. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem because sickling is rare in peripheric blood samples of patients with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced prolonged endothelial inflammation, edema, and fibrosis mainly at the capillary level terminate with cellular hypoxia all over the body (3-5). Capillary vessels are mainly involved in the process due to their distribution function for the hard RBCs. We tried to understand whether or not there is a prolonged survival with the increased number of RBC supports in the SCDs in the present study.

Materials and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and February 2016. All patients with the SCDs were studied. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units in their lives, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Cases with prominent teeth loss (8 or more) were detected. Cases with acute painful crisis or another inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (6). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (7). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (8). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination, hepatic function tests, ultrasonographic results, and tissue sample in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). An exercise electrocardiogram is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Avascular necrosis of bones is diagnosed by means of MRI (11). Stroke is diagnosed by the computed tomography of brain. Ophthalmologic examination was performed according to the patients' complaints. Eventually as one of the significant endpoints of the SCDs, cases with COPD and without were collected into the two groups, and they were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 428 patients with the SCDs (207 females and 221 males) during the nine-year follow-up period. There were 71 patients (16.5%) with COPD. Mean age of the patients was significantly higher in the COPD group (32.8 versus 29.8 years, P=0.005). The male ratio was significantly higher in the COPD group, too (78.8% versus 46.2%, P<0.001). Smoking (35.2% versus 11.4%, P<0.001) and alcohol consumption (7.0% versus 1.9%, P<0.01) were also higher among the COPD cases. Prevalences of associated thalassemia minors were similar in both groups (76.0% versus 68.6% in the COPD group

and other, respectively, P>0.05) (Table 1). Beside these, priapism (14.0% versus 3.0%, P<0.001), cirrhosis (8.4% versus 3.3%, P<0.05), leg ulcers (23.9% versus 12.0%, P<0.01), digital clubbing (25.3% versus 6.7%, P<0.001), CHD (23.9% versus 13.7%, P<0.05), CRD (15.4% versus 7.0%, P<0.01), and stroke (16.9% versus 8.1%, P<0.01) were all higher in the COPD group. Additionally, painful crises per year (5.3 versus 4.9), ileus (4.2% versus 3.9%), prominent teeth loss (4.2% versus 3.0%), pulmonary hypertension (12.6% versus 12.0%), varices (11.2% versus 5.3%), rheumatic heart disease (7.0% versus 6.1%), sinus arrhythmia (4.2% versus 3.0%), and mortality (8.4% versus 6.4%) were all higher among the COPD cases, too but the differences were nonsignificant probably due to the small sample size of the COPD group. Parallel to the above consequences, mean transfused RBC units in their lives were significantly higher among the COPD cases (63.8 versus 33.0, P=0.003). Probably due to the higher number of transfused RBC units in their lives, the mean age of mortality was significantly higher in the COPD group (38.3 versus 30.4 years, P=0.04) (Table 2). On the other hand, there was one patient (1.4%) with HBsAg positivity in the COPD group and 4 patients (1.1%) among the others (P>0.05), but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV positivity was similar in both groups (4.2% versus 6.1% of the COPD patients and others, respectively, P>0.05), HCV RNA positivity was significantly higher in the COPD group (2.7% versus 0.5% of the COPD group and other, respectively, P<0.05) by PCR. On the other hand, there were three patients with the sickle cell retinopathy in the group without COPD.

Table 1: Characteristic features of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Prevalence	16.5% (71)		83.4% (357)
Male ratio	*78.8% (56)*	*<0.001*	*46.2% (165)*
Mean age (year)	*32.8 ± 10.0 (5-58)*	*0.005*	*29.8 ± 9.9 (6-59)*
Thalassemia minors	76.0% (54)	Ns†	68.6% (245)
Smoking	*35.2% (25)*	*<0.001*	*11.4% (41)*
Alcoholism	*7.0% (5)*	*<0.01*	*1.9% (7)*

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05)

Table 2: Associated pathologies of the study cases

Variables	Cases with COPD*	P-value	Cases without COPD
Painful crises per year	5.3 ± 7.9 (0-36)	Ns†	4.9 ± 7.9 (0-52)
Transfused RBC‡ units	***63.8 ± 85.1 (0-434)***	***0.003***	***33.0 ± 39.7 (0-250)***
Priapism	***14.0% (10)***	***<0.001***	***3.0% (11)***
Ileus	4.2% (3)	Ns	3.9% (14)
Prominent teeth loss	4.2% (3)	Ns	3.0% (11)
HCV RNA positivity	***2.7% (2)***	***<0.05***	***0.5% (2)***
Cirrhosis	***8.4% (6)***	***<0.05***	***3.3% (12)***
Leg ulcers	***23.9% (17)***	***<0.01***	***12.0% (43)***
Pulmonary hypertension	12.6% (9)	Ns	12.0% (43)
Varices	11.2% (8)	Ns	5.3% (19)
Digital clubbing	***25.3% (18)***	***<0.001***	***6.7% (24)***
CHD§	***23.9% (17)***	***<0.05***	***13.7% (49)***
CRD¶	***15.4% (11)***	***<0.01***	***7.0% (25)***
Rheumatic heart disease	7.0% (5)	Ns	6.1% (22)
Avascular necrosis of bones	21.1% (15)	Ns	25.2% (90)
Sinus arrhythmia	4.2% (3)	Ns	3.0% (11)
ACS**	1.4% (1)	Ns	3.6% (13)
Stroke	***16.9% (12)***	***<0.01***	***8.1% (29)***
Mortality	8.4% (6)	Ns	6.4% (23)
Mean age of mortality	***38.3 ± 6.9 (31-47)***	***0.04***	***30.4 ± 8.6 (19-50)***

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05) ‡Red blood cell
§Coronary heart disease Chronic renal disease **Acute chest syndrome

Discussion

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of aging and mortality in human beings. Physical inactivity, weight gain, smoking, alcohol, prolonged infections, and chronic inflammatory processes including SCDs, rheumatologic disorders, and cancers may accelerate the process. Probably whole afferent vasculature including capillaries are mainly involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent micro-injuries on endothelium. Thus the term of venosclerosis is not as famous as arteriosclerosis or atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases BP further. Although early withdrawal of causative factors may delay final consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, endothelial changes cannot be reversed completely due to the fibrotic nature of them (12).

SCDs are life-threatening hereditary disorders nearly affecting 100,000 individuals in the United States (13). As a difference from other causes of chronic endothelial damage, they probably keep vascular endothelium particularly at the capillary level (14), since the capillary system is the main distributor of the hard RBCs to the tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in younger ages of the patients. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (15), whereas they were 33.6 and 30.8 years in the present study, respectively. The great differences may be due to delayed diagnosis of the diseases, delayed initiation of hydroxyurea therapy, and inadequate RBC supports in severe clinical conditions in our country. Actually, RBC supports must be given whenever there is evidence of clinical deterioration in the patients (16, 17). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow about the production of abnormal RBCs. So they decrease sickling induced endothelial damage of organs in crises. According to our nine-year experience, simple and repeated transfusions are superior to RBC exchange. First of all, preparation of one or two units of RBC suspensions each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusions of one or two units of RBC suspensions each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions each time by means of simple transfusions will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange. On the other hand, longer lifespan of females in the SCDs (15) and longer overall survival of females in the world (18) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by physical power requiring role of males that may terminate with an exaggerated sickling and atherosclerosis all over the body (19).

COPD is the third leading cause of mortality with different underlying etiologies in the world (20). It is an inflammatory disorder mainly affecting the pulmonary vasculature, and smoking, excess weight, and aging may be the major causes. Regular alcohol consumption may also take place in the inflammatory process. For example, the prevalence of alcohol consumption was significantly higher in the COPD group (7.0% versus 1.9%, $P<0.01$), here. Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study (21). Additionally, 30-day readmission rate was higher in COPD patients with alcoholism (22). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of COPD. The endothelial process is enhanced with release of various chemicals by inflammatory cells, and terminates with endothelial fibrosis and tissue loss in lungs. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of disseminated endothelial inflammation all over the body (23, 24). For example, close relationships were shown between COPD, CHD, PAD, and stroke (25). Similarly, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in smokers in a multi-center study (26). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (26). In another study, 27% of all mortality was due to the cardiovascular causes in the moderate and severe COPD cases (27). Due to the strong atherosclerotic natures of the SCDs and COPD, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalence of priapism, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke in the COPD group, here.

Painful crises are the most disabling and nearly pathognomonic symptoms of the SCDs. For example, only 11.9% of the study cases (9.8% versus 12.3% in the COPD and other groups, respectively, $P>0.05$) have not had any painful crisis in their lives, here. Although the crises may not be life threatening directly (28), infections are the most common precipitating factors of them. The patients are immunocompromised due to a variety of reasons including a functional and anatomic asplenism, chronic endothelial damage induced end-organ failures, a permanent inflammatory process all over the body, hospitalizations, transfusions, and invasive procedures. Because of the deep immunodeficiency, simple infections may even progress to sepsis in a short period of time. Thus multiorgan failures and mortality are not rare during acute painful crises in them. Similarly, RBC supports may provide adequate tissue oxygenation and immunity, and so prevent intractable pain, dissemination of infections or inflammations, end-organ failures, and mortality during surgical operations, major depressions, and other severe clinical conditions. On the other hand, pain is the result of a yet poorly understood interaction between the hard

cells, endothelial cells, white blood cells (WBC), and platelets (PLT). The adverse effects of WBCs and PLTs on endothelium are of particular interest. For example, leukocytosis even at the silent period was an independent predictor of severity of the SCDs (29), and it was associated with an increased risk of stroke (30). On the other hand, leukocytosis and thrombocytosis are acute phase reactants that are also present during the silent periods in the SCDs. They indicate presence of a permanent inflammatory process initiating at birth. The continuous inflammatory process alone causes an additional accelerated atherosclerotic process and a relative weight loss in the SCDs (31). Occlusions of vasculature of the bone marrow, bone infarctions, releasing of inflammatory mediators, and activation of afferent nerves may take a role in the pathophysiology of the intractable pains. Because of the severity of pain, narcotic analgesics are usually required to control them (32), but according to our practice, RBC supports are highly effective during severe crises both to relieve pain and to prevent sudden deaths secondary to the multiorgan failures developed on chronic inflammatory background of the SCDs.

Probably parallel to severity of the inflammatory process, an asplenism develops with decreased antibody production, prevented opsonization, and reticuloendothelial dysfunction due to the repeated infarctions and subsequent fibrosis in early years of life. Similarly, the prevalence of autosplenectomy was 51.6% (221 cases) among the patients with an average age of 30.3 ± 10.0 years (range 5-59), here. Terminal consequence of the asplenism is an increased risk of infections, particularly due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis like encapsulated bacteria. Thus, infections particularly the pneumococcal infections are common in early childhood, and they are associated with a high mortality rate. The causes of mortality were infections in 56% of infants in a previous study (29). In another study, the peak incidence of mortality occured between 1 to 3 years of age in children, and the deaths were predominantly caused by pneumococcal sepsis in patients less than 20 years of age (33). According to our nine-year experiences in adults, patients even who appear relatively fit are susceptible to sepsis, multiorgan failures, and sudden death during acute painful crises due to the deep immunosuppression in them.

ACS is responsible for considerable mortality, particularly during the childhood in the SCDs (34). It occurs most often as a single episode, and a past history is associated with an early mortality (34).

Similarly, all of 14 cases with the ACS had only a single episode, and two of them in the group without COPD were fatal in spite of rigorous RBC, ventilation, and antibiotic supports in the present study. The remaining 12 patients are still alive without a recurrence at the end of the nine-year follow-up period. ACS is the most common between the ages of 2 to 4 years, and its incidence decreases with age (35). Parallel to the knowledge, its incidence was only 3.2% among the patients with an average age of 30.3 years, here. The decreased incidence with aging may be due to a high mortality during the first episode and/or an acquired immunity against various antigens with aging. On the other hand, ACS may also show inborn severity of the SCDs. For example, its incidence is higher in severe cases such as cases with sickle cell anemia (HbSS) and a higher WBC count (34, 35). Probably, ACS is a complex event, and the terminology of 'ACS' does not indicate a definite diagnosis but reflects clinical difficulty of defining a distinct etiology in the majority of such episodes. One of the major clinical problems lies in distinguishing between infection and infarction, and in establishing clinical significance of fat embolism. For example, ACS did not show an infectious etiology in 66% of episodes in the above studies (34, 35). Similarly, 12 of 27 episodes of ACS had evidence of fat embolism as the cause in another study (36). But according to our experiences, the increased metabolic rate during severe infections may terminate with the ACS. In other words, ACS may be characterized by the hard RBCs-induced disseminated endothelial damage and fat embolism at the capillary level. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs (37) indicating a significant reduction of ACS episodes with hydroxyurea suggests that a substantial number of episodes are secondary to the endothelial inflammation and edema at the capillary level. Similarly, we strongly recommend hydroxyurea therapy for all patients at any age that may also be a cause of the low incidence of ACS among our follow-up cases, here. Hydroxyurea is the only drug that was approved by Food and Drug Administration for the treatment of SCDs (13). It is an oral, cheap, safe, and highly effective drug for the SCDs that blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA (13). Its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs (14). Although presence of a continuous damage of hard RBCs on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs as in the autoimmune disorders (14). Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (38). According to our experiences, hydroxyurea is an effective drug for prevention or delay of terminal consequences of the SCDs if it is initiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls in nearly all organs later in life.

As a conclusion, SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. RBC supports in severe clinical conditions probably prolong the survival of patients.

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