

# Low-dose aspirin should be initiated for sickle cell patients

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## ABSTRACT

**Background:** We tried to understand whether or not there is an association between platelet (PLT) count of peripheric blood and severity of sickle cell diseases (SCDs).

**Methods:** SCDs patients with red blood cell (RBC) transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups.

**Results:** The study included 224 patients (70.8%) in the first and 92 patients (29.1%) in the second groups ( $p<0.001$ ). Mean ages were similar in both groups (28.9 and 30.0 years, respectively,  $p>0.05$ ). Male ratio was significantly higher in the second group (45.5% versus 64.1%,  $p<0.001$ ). Although smoking was also higher in the second group (12.0% versus 17.3%,  $p>0.05$ ), the difference was nonsignificant probably due to the small sample size of the second group. Mean units of transfused RBCs were 12.9 and 99.0 in the groups ( $p<0.000$ ). Although white blood cell and PLT counts of peripheric blood were higher in the second group, the difference was only significant for the PLT counts ( $p=0.005$ ), probably due to the same reason above. Number of painful crises per year, digital clubbing, chronic obstructive pulmonary disease, leg ulcers, stroke, chronic renal disease, and coronary heart disease were higher in the second group, significantly ( $p<0.05$  for all).

**Conclusion:** SCDs are chronic inflammatory processes on endothelium mainly at the capillary level, and there was a highly significant association between PLT count and severity of the SCDs. So low-dose aspirin will probably be beneficial for patients with SCDs.

**Key words:** Sickle cell diseases, low-dose aspirin, chronic endothelial damage, atherosclerosis

## Introduction

Atherosclerosis may be the major cause of aging by inducing tissue hypoxia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in the process. Some of the currently known accelerator factors of the obliterative process are physical inactivity, overweight, and smoking for the development of irreversible consequences including obesity, hypertension, diabetes mellitus (DM), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Similarly, sickle cell diseases (SCDs) are chronic inflammatory processes on endothelium mainly at the capillary level. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shapes of RBCs is the major problem, since sickling is very rare in the peripheral blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but it is exaggerated with increased metabolic rate of the body. The hardened cells induced prolonged endothelial inflammation, edema, remodeling, and fibrosis mainly at the capillary level terminate with disseminated tissue infarcts all over the body (4,5). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is an association between platelet (PLT) count of peripheral blood and severity of SCDs in the present study.

## Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and January 2014. All patients with the SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including numbers of painful crises per year, mean units of transfused RBC in their lives, smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. 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, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (6). Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase.

Stroke is diagnosed by the computed tomography of brain. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (7). CRD is diagnosed with a permanent creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females during the silent period. Cirrhosis is diagnosed with liver function tests, ultrasonographic findings, and histologic procedure 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 (8,9). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. A stress electrocardiography is performed just for cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Eventually, cases with RBC transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups, and the groups 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 316 patients with the SCDs (155 females and 161 males). There were 224 patients (70.8%) in the first and 92 patients (29.1%) in the second groups ( $p < 0.001$ ). The mean ages of the groups were similar (28.9 and 30.0 years, respectively,  $p > 0.05$ ). Interestingly, the male ratio was significantly higher in the second group (45.5% versus 64.1%,  $p < 0.001$ ). Although the prevalence of smoking was also higher in the second group (12.0% versus 17.3%), the difference was nonsignificant probably due to the small sample size of the second group ( $p > 0.05$ ). There was a nonsignificant difference according to the prevalence of associated thalassemia minors ( $p > 0.05$ ). The mean units of transfused RBCs were 12.9 and 99.0 in the first and second groups, respectively ( $p < 0.000$ ) (Table 1). Although both the WBC and PLT counts of the peripheral blood were higher in the second group, the difference was only significant for the PLT counts ( $p = 0.005$ ), probably due to the small sample size of the second group again. Mean hematocrit values were similar in the first and second groups (23.8% versus 23.7%, respectively,  $p > 0.05$ ) (Table 2). Although the prevalences of avascular necrosis of bones, cirrhosis, and exitus were similar in both groups ( $p > 0.05$  for all), the mean number of painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were significantly higher in the second group ( $p < 0.05$  for all) (Table 3). Mean ages of the mortal cases were  $29.5 \pm 9.8$  (19-50) and  $34.6 \pm 6.7$  (26-44) years in the first and second groups, respectively ( $p > 0.05$ ). Mean ages of the mortal cases were  $29.7 \pm 9.6$  (19-50) and  $33.3 \pm 8.5$  (21-44) years in males and females, respectively ( $p > 0.05$ ). On the other hand, there was no patient with regular alcohol consumption among the study cases. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both.

Table 1: Sickle cell patients with the units of red blood cell transfusions

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
<b>Prevalence</b>	<b><u>70.8% (224)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>29.1% (92)</u></b>
Mean age (year)	28.9 ± 9.9 (5-59)	Ns†	30.0 ± 9.2 (9-56)
<b>Male ratio</b>	<b><u>45.5% (102)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>64.1% (59)</u></b>
Smoking	12.0% (27)	Ns	17.3% (16)
Thalassemia minors	62.0% (139)	Ns	58.6% (54)
<b>Mean RBC units</b>	<b><u>12.9 ± 11.2 (0-48)</u></b>	<b><u>&lt;0.000</u></b>	<b><u>99.0 ± 56.5 (50-362)</u></b>

\*Red blood cell †Nonsignificant (p>0.05)

Table 2: Sickle cell patients with peripheric blood values

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
Mean WBC† count (μL)	14.931 ± 6.791 (2.460-39.200)	Ns‡	15.346 ± 5.640 (1.580-36.900)
<b>Mean PLT§ count (μL)</b>	<b><u>435.670 ± 236.693 (48.000-1.827.000)</u></b>	<b><u>0.005</u></b>	<b><u>498.310 ± 224.570 (53.000-1.370.000)</u></b>
Mean hematocrit value (%)	23.8 ± 4.8 (11-42)	Ns	23.7 ± 4.9 (13-39)

\*Red blood cell †White blood cell ‡Nonsignificant (p>0.05) §Platelet

Table 3: Sickle cell patients with associated disorders

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
<b>Painful crises per year</b>	<b><u>3.8 ± 6.3 (0-52)</u></b>	<b><u>0.000</u></b>	<b><u>8.4 ± 10.9 (0-52)</u></b>
<b>Digital clubbing</b>	<b><u>7.1% (16)</u></b>	<b><u>&lt;0.01</u></b>	<b><u>15.2% (14)</u></b>
<b>COPD‡</b>	<b><u>6.6% (15)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>20.6% (19)</u></b>
<b>Leg ulcers</b>	<b><u>11.6% (26)</u></b>	<b><u>&lt;0.01</u></b>	<b><u>21.7% (20)</u></b>
<b>Stroke</b>	<b><u>5.8% (13)</u></b>	<b><u>&lt;0.05</u></b>	<b><u>11.9% (11)</u></b>
<b>CRD§</b>	<b><u>4.9% (11)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>14.1% (13)</u></b>
Avascular necrosis of bones	20.5% (46)	Ns	17.3% (16)
Cirrhosis	4.4% (10)	Ns	4.3% (4)
<b>CHD¶</b>	<b><u>4.0% (9)</u></b>	<b><u>&lt;0.05</u></b>	<b><u>8.6% (8)</u></b>
Exitus	4.4% (10)	Ns	5.4% (5)

\*Red blood cell †Nonsignificant (p>0.05) ‡Chronic obstructive pulmonary disease §Chronic renal disease ¶Coronary heart disease

## Discussion

Chronic endothelial damage and atherosclerosis is the most common type of vasculitis, and the leading cause of morbidity and mortality in elderlies. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected due to the much lower BP in them. Secondary to the prolonged endothelial damage and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures which can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including smoking, physical inactivity, excess weight, increased serum glucose and lipids, and elevated arterial BP may prevent terminal consequences, after development of COPD, cirrhosis, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic natures of them (10).

SCDs are life-threatening genetic disorders affecting nearly 100,000 individuals in the United States (11). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium mainly at the capillary level (12), since the capillary system is the main distributor of the hardened RBCs to tissues. The hardened cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (13), whereas they were 33.3 and 29.7 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC transfusions in emergencies in our country. On the other hand, longer lifespan of females with the SCDs and longer overall survival of females in the world can not be explained by the atherosclerotic effects of smoking alone, instead it may be explained by physical power requiring role of male sex in life (14,15), since physical power induced increased metabolic rate may terminate with an exaggerated sickling and atherosclerosis in human body.

Painful crises are nearly pathognomonic for the SCDs, and precipitated by infections, operations, depressions, and disseminated tissue damage. Although painful crises may not be life threatening directly (16), increased metabolic rate may terminate with multiorgan failures on the chronic inflammatory background of the SCDs (17). The severe pain may be secondary to the disseminated inflammation of the capillary endothelium, and the increased WBC and PLT counts and decreased hematocrit values may show presence of a chronic inflammatory process during whole their lives in such patients in the present study. Similar to us, increased WBC counts even in the absence of a painful crisis was an independent predictor of the disease severity (18), and it was associated with an increased risk of stroke by causing disseminated endothelial damage in brain (19). Due to the severity of pain, narcotic analgesics are usually required (20), 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 death that may develop secondary to the multiorgan failures on the chronic inflammatory background of the SCDs. Simplicity of preparation of RBC suspensions in a short period of time pro-

vides advantages to clinicians to use them even in small public hospitals without the requirement of specialized health workers and equipments as in RBC exchange. Additionally, preparation of one or two units of RBC suspension in each time provides time to clinicians to prepare more units by preventing sudden death of the patients. By this way, we can prevent some of deaths developed during transport of severe cases to tertiary health centers.

Hydroxyurea is an effective drug in chronic myeloproliferative disorders and SCDs (12). It interferes with cell division by blocking the formation of deoxyribonucleotides which are building blocks of DNA. Although the action way of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (HbF) (21,22), its main action may be suppression of hyperproliferative WBC and PLTs in the SCDs. As in autoimmune disorders, although presence of a continuous damage of hardened RBCs on endothelium, the severity of endothelial destruction is probably exaggerated by the patients' own WBCs and PLTs in the SCDs. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferative skin cells. Similarly, 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 (23). On the other hand, final HbF levels in hydroxyurea users did not differ from their pretreatment levels, significantly (23). Similarly, the Multicenter Study of Hydroxyurea studied 299 severely involved adults with sickle cell anemia (HbSS), and compared the results of patients treated with hydroxyurea or placebo (24). The study especially searched effects of the drug on painful crises, acute chest syndrome, and requirement of RBC transfusions. The results were so overwhelming in the 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 an independent association of lower neutrophil counts with the lower crisis rates (24). But this study was performed in severe HbSS cases alone, and the mean number of painful crises was decreased from 4.5 to 2.5 per year (24). Whereas in one of our studies, we studied 337 patients with all subtypes and severities of the SCDs, and the mean number 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, degree of severity according to patient's self-explanation between 0 and 10,  $p < 0.000$ ) (25). Additionally, adult SCDs patients using hydroxyurea appear to have a reduced mortality rate after a 9-year follow-up period (26). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may decrease severity of disease (26) and prolong survival (12). Furthermore, 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 incidences of them (27). Hydroxyurea in early years of life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions. Transfusion programmes can also reduce the complications, but they carry some major risks including infections, development of allo-antibodies, and iron overload. Beside that, using an oral drug is a much more easier method than the regular blood transfusions for the patients, families, health workers, and insurance systems.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), but differs from most others in the mechanism of action, since only low-doses of aspirin (75-100 mg/day) exert protective vascular effects (28). Although aspirin and other salicylates have similar effects (analgesic, antipyretic, and anti-inflammatory) with the other NSAIDs and inhibit the same enzyme cyclooxygenase (COX), aspirin does so in an irreversible manner and, unlike others, affects more the COX-1 than the COX-2 variants of the enzyme. It inhibits the production of thromboxane, which is significant for building of a patch over damaged blood vessels. Because the patch can become too large and block blood flow extensively, aspirin is also used at low-doses to prevent heart attacks, strokes, and other thromboembolic events. Additionally, low-doses of aspirin are usually given just after a heart attack to reduce the risk of progression or development of others. A review of data regarding aspirin use for secondary prevention of acute coronary syndromes demonstrated that low-doses of aspirin are consistently favored for short- and long-term use due to the lack of a dose-response relationship between increasing the dose and improved efficacy, and a higher incidence of gastrointestinal bleeding with increasing the dose (28,29). Women aged 65 years and older without any established cardiovascular disease, women of any age with established cardiovascular disease, and women of any age with an estimated 10-year risk of cardiovascular disease of 10% or higher are likely to experience a benefit from low-doses of aspirin (30). Low-doses of aspirin have been shown to be effective in prevention of one-fifth of thromboembolic events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in a meta-analysis of 16 secondary prevention trials in patients with previous myocardial infarction, stroke, or transient cerebral ischemia. This corresponds to an absolute reduction of about 10-20 per 1,000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death (31). So the benefits of antiplatelet therapy substantially exceed the risk for secondary prevention (31), and use of low-doses of aspirin reflects good clinical practice and is encouraged in current guidelines (29).

As a conclusion, SCDs are chronic inflammatory processes on endothelium mainly at the capillary level and there was a highly significant association between PLT count and severity of the SCDs. So low-dose aspirin will probably be beneficial for patients with the SCDs.

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