Annals of Yoga and Physical Therapy

Open Access

Austin Publishing Group

Research Article

Impact of Aerobic Exercises on Coagulation Profile, Platelets and Endothelial Activation Markers among Patients with Steady State Sickle Cell Anemia

Abd El-Kader SM[1]*, Al-Jiffri OH[2] and Alsharif FM[2]

[1]Department of Physical Therapy, King Abdulaziz University, Saudi Arabia

[2]Department of Medical Laboratory Technology, King Abdulaziz University, Saudi Arabia

***Corresponding author:** Shehab M. Abd El-Kader, Department of Physical Therapy, Faculty of Applied Medical Sciences, King Abdulaziz University, P.O. Box 80324, Jeddah, 21589, Saudi Arabia

Received: January 09, 2017; **Accepted:** January 31, 2017; **Published:** February 02, 2017

Abstract

Background & Objective: Globally, Sickle Cell Anemia (SCA) causes multiple organ damage resulted from small blood vessels that leads to many vascular complications as acute chest syndrome, cerebral vascular accidents and avascular necrosis.

Objective: As the available previous studies involving the impact of exercise training upon patients with SCA is still scarce and not clear; this study designed to measure the actual value of aerobic exercise upon some coagulation profile, platelets and endothelial activation markers among patients with steady state SCA.

Material and Methods: Eighty patients with steady state condition sickle cell anemia were enrolled in two equal groups; the first group practiced aerobic exercises for three months, while the second group was considered as a control group as they received no training intervention.

Results: The mean values of coagulation profiles included PT, APTT and platelet count (P=0.016, P=0.008, P=0.027 respectively), platelets activation markers included soluble CD40L and soluble P-Selectin (P=0.001, P=0.011 respectively) and endothelial activation markers included ICAM-1, VCAM-1and E-selectin (P=0.002, P=0.016, P=0.021 respectively) were reduced significantly as a result of aerobic exercise training in group (A), with no significant changes in the control group (group B). In addition, at the end of the study, the comparison between both groups revealed that significant differences ($p<0.05$).

Conclusion: The current study provides evidence that aerobic exercise training improves prolonged coagulation indices and altered markers of platelets and endothelial activation among patients with SCA in asymptomatic steady state.

Keywords: Coagulation profile; Platelets activation markers; Endothelial activation markers; Aerobic exercise; Sickle cell anemia; Steady state

Introduction

Sickle Cell Anemia (SCA) is a hematologic disorder leads to multiple organs irreversible damage [1]. However, recurrent vascular occlusion and chronic hemolysis that enhanced by leukocyte and red blood cells adhesion has been reported in patients with SCA [2]. Moreover, disorders of blood coagulation profile, abnormal inflammatory cytokines and endothelial dysfunction were found to be associated with SCA [1,3,4]. The severity of clinical presentation ranges from mild degree to life-threatening degree [5].

Sickle cell disease is characterized with prolonged Prothrombin Time (PT) and Activated Thromboplastin Time (APTT) [4,6]. In addition, platelet counts and platelets activation markers (P-selectin and CD40L) are usually increased among SCA in steady state [7-9]. While, endothelial activation biomarkers (Vascular Cell Adhesion Molecule (VCAM)-1, and Intercellular Adhesion Molecule (ICAM)-1 and E-selectin) are usually elevated among patients with SCA [10-12].

Microvascular occlusion is the main cause of organ damage and recurrent attacked of painful crises in SCA. However, systemic inflammatory stimuli and endothelial dysfunction that induced by sickle cells restrict the microcirculation [13]. More over increased levels of endothelial function biomarkers as Intercellular Adhesion Molecule (ICAM)-1, Vascular Cell Adhesion Molecule (VCAM)-1 and E-selectin play a pivotal role in painful SCA crises [14,15].

However, Sickle cell anemia causes multiple organ damage resulted from small blood vessels that leads to many vascular complications as acute chest syndrome, cerebral vascular accidents and avascular necrosis [13]. Many changes in the hemostatic system in SCA patients have been reported as fibrinolysis activation and excess in thrombin generation [14]. These changes are seen in SCA both in Vaso-Occlusive Crises (VOC) and steady state [16,17]. Some documented abnormalities in fibrinolytic system in SCA include reduced plasminogen concentration [18], elevated D-dimer [19] and defective release of tissue Plasminogen Activator (tPA) [20]. Moreover, excessive thrombin generation, activation of platelet,

Citation: Abd El-Kader SM, Al-Jiffri OH and Alsharif FM. Impact of Aerobic Exercises on Coagulation Profile, Platelets and Endothelial Activation Markers among Patients with Steady State Sickle Cell Anemia. Ann Yoga Phys Ther. 2017; 2(1): 1021.

Table 1: Baseline variables and investigated parameters of all participants.

	Group (A)	Group (B)	P value
Age (year)	36.42 ± 3.15	34.97 ± 4.36	0.621
BMI (kg/m^2)	18.67 ± 4.23	19.14 ± 3.81	0.576
Hemoglobin (g/dL)	7.38 ± 2.72	6.96 ± 2.65	0.198
Red blood cells (10^{12} L)	2.45 ± 1.39	2.37 ± 1.24	0.521
white blood cells (10^9 L)	9.78 ± 3.23	9.44 ± 2.91	0.067
PT (seconds)	13.63 ± 3.15	13.91 ± 3.46	0.216
APTT (seconds)	42.34 ± 6.21	43.12 ± 5.88	0.743
Platelet Count (×10^3)	281.23 ± 40.18	284.37 ± 41.25	0.265
Soluble CD40L (pg/ml)	562.85 ± 61.42	563.29 ± 57.13	0.072
Soluble P-Selectin (ng/ml)	38.14 ± 5.83	40.26 ± 6.15	0.628
ICAM-1	14.95 ± 3.27	15.33 ± 4.02	0.546
VCAM-1	17.86 ± 3.65	18.11 ± 3.85	0.614
E-selectin	4.57 ± 1.28	4.93 ± 1.37	0.385

BMI: Body Mass Index; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CD40L: CD40 Ligand; ICAM-1: Intercellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule.

decreased circulating anticoagulants levels and contact factors has been reported [14].

Regular exercise has a modulating effect for the cardiovascular risk as abnormal coagulation and abnormal changes in the hemostatic system [21,22] as exercise induces a remarkable fibrinolytic activity [23,24].

This study designed to measure the actual value of aerobic exercise upon some coagulation profile, platelets and endothelial activation markers among patients with steady state SCA.

Subjects and Methods

Subjects

Eighty steady state sickle cell anemia Saudi subjects were selected from Department of Hematology, King Abdalaziz University Hospital. Diagnosis of all participants was confirmed by using hemoglobin electrophoresis equipment, however, steady state of Sickle cell anemia was confirmed if the patient did not receive blood transfusion during the previous 120 days and not have acute episodes (vaso-occlusive or infective crisis) for at least 30 days before participation in the study [25]. Exclusion criteria included cancer, hypertension, pregnancy, contraceptive bills, anticoagulant medications, cardiopulmonary disorders, diabetes mellitus and patients received blood transfusion within the previous 120 days. All participants signed a written informed consent and ethical approval from the ethical committee, Faculty of Applied Medical Sciences, King Abdalaziz University has been obtained (FAMS-18-2016). All participants were enrolled equally in group (A) who received training on treadmill and group (B) who was considered as a control group who received no training intervention.

Methods

Measurements:

Determination of coagulation profile: Both plasma level of prothrombin time was detected by adding 0.1 ml of both plasma placed in a water bath to 0.1 ml of thromboplastin and calcium.

Table 2: Mean value and significance of the investigated parameters of group (A) before and at the end of the study.

	Mean ± SD		t-value	P value
	Pre	Post		
PT (seconds)	13.63 ± 3.15	10.11 ± 2.86*	6.12	0.016*
APTT (seconds)	42.34 ± 6.21	34.87 ± 5.13*	7.22	0.008*
Platelet Count (×10^3)	281.23 ± 40.18	226.39 ± 27.46*	8.15	0.027*
Soluble CD40L (pg/ml)	562.85 ± 61.42	387.21 ± 45.13*	10.14	0.001*
Soluble P-Selectin (ng/ml)	38.14 ± 5.83	25.39 ± 4.62*	6.38	0.011*
ICAM-1	14.95 ± 3.27	12.01 ± 3.12*	5.17	0.002*
VCAM-1	17.86 ± 3.65	10.34 ± 2.71*	6.23	0.016*
E-selectin	4.57 ± 1.28	1.91 ± 0.76*	5.11	0.021*

PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CD40L: CD40 Ligand; ICAM-1: Intercellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference between the two groups, P < 0.05.

However, activated partial thromboplastin time in kaolin was detected by mixing equal volumes of kaolin suspension and the phospholipids reagent. Moreover, hemoglobin concentration and platelet count was measured using automated Sysmex KX-21N model [26].

Determination of platelets activation markers: Flow cytometer (FACSCalibur cytometer and CellQuest Pro software, San Jose, CA) was used to determine platelets activation markers. Soluble CD40L (Quantikine Human CD40 Ligand Immunoassay, R&D Systems, Minneapolis, MN) and P-selectin (Human P-Selectin ELISA, R&D Systems, Minneapolis, MN) were assessed in plasma prepared from blood samples collected into Ethylenediaminetetra Acetic Acid (EDTA) and centrifuged at 1000 g for 15 minutes within 30 minutes of collection. Samples for the CD40L assay were centrifuged for an additional 10 minutes at 10,000 g [27,28].

Determination of endothelial activation markers: The serum samples was stored at –80°C to be used by ELISAs in order to measure levels of ICAM-1 and VCAM-1, and E-selectin, (R&D Systems) that considered as endothelial activation markers.

Procedures

Participants were enrolled randomly in two groups:

1. The training group (Group A) patients were submitted to the aerobic exercise training to complete a 12-week on a treadmill (EnrafNonium, Model display panel Standard, NR 1475.801, Holland). Each session of physical exercise was divided in: 5 min of warm up, with stretching exercises and circling of members and body; 30 min of aerobic exercise divided into row ergometer (15 min) and bicycle ergometer (15 min).; and 5 min of cold down at the end, with stretching, flexibility and relaxation exercises, consisting of five sessions per week. The training program was performed at 70% of the individual age-predicted HRmax according to Tanaka, et al. [29].

2. The control group (B) received no training intervention.

Statistical analysis

Analytical analysis was conducted using paired "t" to compare the investigated parameters obtained before and after three months in both groups, where comparison between both groups was conducted using the independent "t" test (P<0.05).

Table 3: Mean value and significance of the investigated parameters of group (B) before and at the end of the study.

	Mean ± SD		t-value	P value
	Pre	Post		
PT (seconds)	13.91 ± 3.46	14.21 ± 3.77	0.58	0.432
APTT (seconds)	43.12 ± 5.88	43.65 ± 6.02	0.61	0.314
Platelet Count (×10³)	284.37 ± 41.25	292.18 ± 42.34	1.14	0.215
Soluble CD40L (pg/ml)	563.29 ± 57.13	578.52 ± 59.42	1.22	0.265
Soluble P-Selectin (ng/ml)	40.26 ± 6.15	40.93 ± 6.34	0.78	0.671
ICAM-1	15.33 ± 4.02	16.15 ± 4.29	0.49	0.366
VCAM-1	18.11 ± 3.85	18.72 ± 4.03	0.83	0.548
E-selectin	4.93 ± 1.37	5.14 ± 1.58	0.64	0.463

PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CD40L: CD40 Ligand; ICAM-1: Intercellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference between the two groups, $P < 0.05$.

Table 4: Mean value and significance of the investigated parameters of group (A) and group (B) at the end of the study.

	Mean ± SD		t-value	P value
	Group (A)	Group (B)		
PT (seconds)	10.11 ± 2.86*	14.21 ± 3.77	7.25	0.002*
APTT (seconds)	34.87 ± 5.13*	43.65 ± 6.02	7.83	0.024*
Platelet Count (×10³)	226.39 ± 27.46*	292.18 ± 42.34	9.16	0.001*
Soluble CD40L (pg/ml)	387.21 ± 45.13*	578.52 ± 59.42	10.84	0.005*
Soluble P-Selectin (ng/ml)	25.39 ± 4.62*	40.93 ± 6.34	7.15	0.006*
ICAM-1	12.01 ± 3.12*	16.15 ± 4.29	6.28	0.003*
VCAM-1	10.34 ± 2.71*	18.72 ± 4.03	7.13	0.018*
E-selectin	1.91 ± 0.76*	5.14 ± 1.58	6.07	0.015*

PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CD40L: CD40 Ligand; ICAM-1: Intercellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference between the two groups, $P < 0.05$.

Results

Eighty steady state SCA patients participated in the present study, the age was (mean36.42 ± 3.15& range: 26-48year) and (mean 34.97 ± 4.36 and range: 24–49 year) for group (A) and (B) respectively. Regarding the baseline variables, the two groups were considered homogeneous regarding the baseline variables and the investigated parameters (Table 1) and there was no significant difference in hemoglobin, white blood cells and red blood cells between both groups.

The mean values of coagulation profiles (PT, APTT and Platelet count), platelets activation markers (Soluble CD40L and Soluble P-Selectin) and endothelial activation markers (ICAM-1, VCAM-1and E-selectin) were reduced significantly because of aerobic exercise training in group (A) (Table 2), with no significant changes in the control group (Table 3). In addition, at the end of the study the comparison between both groups showed that differences were significant between both groups (Table 4).

Discussion

Microvascular occlusion that includes organ damage and painful crises is a common problem facing patients with SCA [7]. Elevation in platelet activation and thrombin generation along with reduced level of circulating anticoagulants are the main changes in the hemostatic system in SCA [14]. In the other hand, regular activities are of great value in reducing cardiovascular diseases risk factors by modulation of platelet activity and regulation of coagulation [30].

To the best of our knowledge, this is the first research addressing some coagulation profiles (PT, APTT and Platelet count), platelets activation markers (CD40L and P-Selectin) and endothelial activation biomarkers (ICAM-1, VCAM-1 and E-selectin) of patients with SCA following three months of continuous exercise training. We observed significant drop in PT, APTT, platelet count, CD40L, P-Selectin, ICAM-1, VCAM-1 and E-selectin after 3 months of aerobic exercise training among patients with SCA.

Our results agreed with several previous researches where aerobic exercise modulates coagulation profile, platelets and endothelial activation markers. Many investigators reported that exercise training reduces the aPTT [31-35]. However, Menzeland Hilberg stated that there was no relation between the changes in aPTT and the both the duration and the intensity of the exercise [36]. While, Robach, et al. proved that exercise training resulted in drop in the number of platelet [37]. In addition, Wang, et al. reported that short-term exercise on bicycle ergometer led to reduction in platelet aggregation [38]. Moreover, Wang and Liao mentioned that short-term exercise training of moderate intensity resulted in reduced P-selectin expression, platelet aggregation and adhesion [39]. In addition, Yang and colleagues proved that animal ran on a treadmill experienced reduction in the expression of adhesion molecules included P-selectin, VCAM-1, inducible NO Synthase (iNOS) and monocyte chemoattractant protein-1(MCP-1) [40]. While, Zoppini and colleagues found that six months of aerobic exercise training led to reduction in ICAM-1 and P-selectin levels in addition to significant increase in level of HDL-cholesterol among elderly patients with type 2 diabetes mellitus [41]. Finally, Jilma and colleagues stated that after two different training protocols on an ergometry and endurance exercise in healthy untrained men resulted in little change in the levels of E-selectin, VCAM-1 and ICAM-1 [42].

Conclusion

The current study provides evidence that aerobic exercise training improves prolonged coagulation indices and altered markers of platelets and endothelial activation among patients with steady state sickle cell anemia.

Acknowledgment

This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, under grant no. (G-50-142-37). The authors, therefore, acknowledge with thanks DSR for technical and financial support.

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Citation: Abd El-Kader SM, Al-Jiffri OH and Alsharif FM. Impact of Aerobic Exercises on Coagulation Profile, Platelets and Endothelial Activation Markers among Patients with Steady State Sickle Cell Anemia. Ann Yoga Phys Ther. 2017; 2(1): 1021.