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Effect of High-Intensity Interval Training and Crocin on Hematological Parameters in Doxorubicin-Induced Male Rats

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Abstract

Background: Doxorubicin (DOX) is an anthracyclines antibiotic and is one of the most effective antitumor drugs. However, using this drug is associated with poisoning of healthy tissues. The purpose of this study was to investigate the changes in hematological parameters of male rats exposed to doxorubicin after eight weeks of high-intensity interval training and crocin consumption.

Materials and Methods: In the present experimental research, 50 male Wistar rats (weight 200-220 gr) were exposed to intraperitoneal injections of doxorubicin (2mg/kg, seven times for 7weeks) and randomly placed into five groups, including healthy control (saline) group, doxorubin group, doxorubicin with Crocin group, doxorubicin with training group, and doxorubicin with crocin a long with training group. The training groups completed the course with two intense interval training during the first week and completed 8 intense interval training in the last weeks. Forty eight hours after the last training session, blood samples were taken directly from the heart of rats to measure the desired indices of red blood cell (RBC), Hematocrit(HCT), Hemoglobin(HB), platelet(PLT), white blood cell(WBC), and percentage of lymphocytes(%LYM), and neutrophils (%NEU). Independent sample t-test as well as two-way ANOVA were used for data analysis. P value <0.01 was set as significant level.

Results: The results showed that DOX significantly reduced all of the blood parameters in rats in comparison to the control group ($p<0.01$). Eight-week high intensity interval training significantly increased blood parameters ($p<0.01$). In Crocin- treated rats, the blood parameters were significantly increased compared with the DOX-intoxicated animals ($p<0.01$). In Crocin and high intensity interval training group, the blood parameters were significantly increased compared with the DOX-intoxicated animals ($p<0.01$).

Conclusion: It seems that high-intensity interval training, Crocin, as well as combination of these two interventions can prevent severe reduction of hematological parameters in rats treated with doxorubicin.

Keywords: Crocin, Doxorubicin, Hematological Parameters, High intensity interval training

Introduction

According to statistics released by the World Health Organization in 2011, cancer is the second leading cause of death after cardiovascular disease in the world (1). Doxorubicin (DOX) or Adriamycin, as one of the most effective chemotherapy drugs that belongs to the Anthracycline family, is an antibiotic with a wide range of anti-tumor and anti-cancer functions that is widely used in the treatment of cancers (2). However, the clinical use of this drug is limited due to its Cytoxic effects on non-target tissues such as heart, liver, kidney, skeletal muscle, testis (3) and bone marrow(4). This medicine reduces the number of leukocytes (white blood cells), especially in neutrophil counts (neutropenia). It also increases the risk of infection, decreases erythrocytes (hypoxia and fatigue), and decreases platelets; hence, increases inclining to bleeding (2). Chemotherapy also increases the incidence of anemia in cancer patients. In a study on 148 patients undergoing chemotherapy, Kitano showed that 44% of these patients

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had anemia before treatment and the prevalence of anemia among them increased to 84% during the chemotherapy. Also, 72% of patients who were not anemic before developed anemia during chemotherapy (5).

Reduction of white blood cells during chemotherapy is a serious hindrance to the continuation of treatment and delayed chemotherapy (6). In patients with various cancers, anemia increases the risk of death by as much as 65% (7, 8). Anemia treatment can influence the patient's response to cancer and the progression of the disease (9).

Today, physical activity, in addition to maintaining health and well-being, is one of the complementary therapies in many diseases. There is an undeniable evidence of the effect of regular physical training on primary and secondary prevention of many chronic diseases such as cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis (10). Physical activity is one of the many known lifestyle factors that reduce the risk of cancer. There is increasing and convincing evidence that physical activity, especially in surveillance programs, reduces many common adverse effects of cancer amongst survivors, and generally improves the quality of life in these individuals (11-14).

Some studies show that aerobic activity increases the amount of erythrocytes, especially hemoglobin, over the course of treatment and after chemotherapy (15). With physical activities, the number of red blood cells and white blood cells, and in general, the blood volume and blood elements involved in the immune system increase and this contributes to the better functioning of the immune system (16).

Developing evidence suggests that high intensity interval training provides comparable physiological adaptations with moderate intensity training with low time and overall activity reduction (17). These findings are important from the perspective of public health because "shortage of time" is one of the most common barriers to regular participation in physical activity (18,19). In addition, recent evidence suggests that HIIT is more enjoyable than a moderate intensity training (20). Generally, high intensity interval training is defined as an activity that is performed at frequencies close to the maximum intensity and usually at an intensity exceeding 80% of the maximum heart rate (often at an intensity of 0.85 to 0.95)(21).

These extreme frequencies are separated by a few minutes of rest or activity with a low intensity, which leads to a slight return to the initial state (22).

In addition to physical activity, over the past two decades, medicinal plants have been investigated with effective anticancer activity, and the use of herbal medicines in cancer patients is also increasing to reduce the side effects or increase the efficacy of chemotherapy drugs (23, 24). Various studies have shown that some antioxidant compounds increase tumor response to chemotherapy, reduce the adverse effects of anticancer drugs, or reduce the toxicity of chemotherapy in normal cells (25). Crocin is the most important carotenoid in saffron which has anti-anemiac properties (26). According to previous research, Crocin may potentially have anti-tumor effects and improve the side effects of chemotherapy (27). It has also been shown that Crocin inhibits the growth of cancer cells significantly without side effects in normal cells (28).

Considering the potential of physical activity and herbal medicines in the prevention and treatment of many diseases, the use of a suitable and combined strategy for the synergistic effect of these two interventions in preventing or treating cancer and reducing the side effects of chemotherapy seems necessary. Accordingly, due to dearth of scientific information on the simultaneous effect of implementation of severe aerobic interval activity along with crocin consumption on the hematological properties of doxorubicin-induced rats, the aim of this

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study was to elucidate the effect of high intensity interval training and crocin consumption on hematological parameters in male rats treated with doxorubicin.

Materials and Methods

Animal care

In the present experimental study, 50 male Wistar rats (8-week-old, weighing 200±220 gr) were investigated. The rats were purchased from Jondishapur University of Ahvaz. The rats were kept in standard cages at room temperature (22±3°C), regular cycle (12 light/12 dark), humidity of 35 ± 5° with proper ventilation, and free access to food and water. Before randomization, all rats were lightly exercised on the treadmill (8-10 m/min) for 5-10 min/day for 10 days to acclimatize them to the treadmill and protocol; however, it was not the same as our main training protocol.

After two weeks of familiarization with the environment and the way of doing activity, the rats were divided into five groups: 1) healthy control (saline) group, 2) doxorubin group, 3) doxorubicin with crocin group, 4) doxorubicin with training group, and 5) doxorubicin with crocin along with training group. All of the ethical standards were observed based on the ethical standards of Animal Physiology Laboratory, Shahid Chamran University.

Exercise training protocol

The rats in the training groups were forced to run on a non-slip motorized rodent treadmill at two-minute intervals, five days a week for 8 weeks. During the training protocol, the heating and cooling steps were performed at the beginning and end of each main training session with intensity of 40% to 50% of maximum speed (16-20m/min) for 5 minutes. The main training included 2 intervals with an intensity of 80%(32m/min) of the maximum speed in the first week; 4 intervals with 85% (34m/min) of the maximum speed in the second week; and 6 intervals with 90%(36m/min) of the maximum speed since the beginning of the third week, which was sustained by the end of the period, but at the beginning of the fourth week until the end of the period, there were 8 severe intervals. Low intensity intervals included two minutes of intensity 40% (16 m/min) of maximum speed from the first week to the end of the third week and 30% (12 m/min) of the maximum speed from the beginning of the fourth week to the end of the period. Therefore, the total time of the exercise in the first week was 16 minutes, the second week 24 minutes, the third week 32 minutes, and from the beginning of the fourth week to the end of period was 40 minutes. This protocol was designed according to the protocol suggested by Rezaei *et al.* (2015). Due to the side effects of doxorubicin on the performance of rats, training intensity was adjusted, hence at the beginning of each week their maximum speed was calculated and the intensity of training based on that was adjusted (29). The rats in the control group were left on the treadmill without running for the same time period as the training groups.

Chemicals

Crocin was purchased as a powder from the Sigma-Aldrich Co (St. Louis, MO, USA) in five gr vials with a purity of 98%. The crocin group and the crocin and training group received 10mg/kg crocin dissolved in 10 ml/kg normal saline, by oral gavage on training days for 8 weeks. The health (control) and doxorubicin groups received the same amount of normal saline as gavage (30).

Doxorubicin was purchased from the Belgian Abve Company and the rats were treated with sub-chronic protocol of seven weekly injections with doxorubicin rarefied with normal saline (NaCl 0.9%) (intraperitoneal injection 2 mg/kg of body weight, cumulative dose of 14 mg/kg). The animals assigned to the groups received doxorubicin or saline injections during the weekend in the day-off training (Friday morning: 48 h after the last training session and 24 h before the next one). In

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order to prevent the effects of the round-the-clock program, all injections were homogeneous and done around 10 in the morning (31).

Sample Collection

Forty-eight hours after the final training session, all rats were anesthetized by intraperitoneal injection with a combination of ketamine and xylazine (90 and 10 mg/kg body weight, respectively). Blood samples were collected using anticoagulant tubes of ethylene diamine tetraacetic acid (EDTA) by cardiac puncture from all rats, and immediately transferred to the laboratory for evaluation of hematological factors. Red blood cells (RBC), Hematocrit(HCT), Hemoglobin(Hb), White blood cells(WBC), Lymphocyte and Neutrophil ratio, and Platelet count (PLT) were measured using Hematology Analyzer (Sysmex cell counter KX21, Japan).

Statistical Analysis

All data were analyzed using SPSS 21. Shapiro-wilk and Levene's tests were used to determine the normality of all data and the variance of the groups. To examine the difference between the healthy (control) group and the doxorubicin group (the effect of drug injection), independent sample t-test was used. Two-way ANOVA was used to measure the effect of training and crocin. Where the P values were significant, Tukey's post-hoc test was used to test the differences between the groups. The significance level was considered to be less than 0.05 for all statistical analyses.

Results

Table I presents the hematological parameters of healthy control and experimental groups, after induction of doxorubicin and implementation of 8 weeks exercise and receiving crocin.

Results showed that chronic treatment with doxorubicin caused a significant decrease in all blood parameters (RBC, Hb, HCT, WBC, lymphocyte and neutrophil ratio and PLT) in experimental groups compared to the healthy control group ($p<0.05$) (Table II). Also, the results of two-way ANOVA test showed that the implementation of 8 weeks of high intensity interval training, consumption of crocin as well as a combination of these two interventions significantly increased all blood indices in experimental groups compared to the control group (doxorubicin) (Table II). It was also found that although there was a difference between the effect of crocin and high intensity interval training on increasing blood indexes, this difference was not significant. In addition, it was found that there was a significant difference between the combined effect of crocin and high intensity interval training and the effect of each of these two interventions alone on blood indices of the experimental groups compared to the control group, and these two interventions strengthened the effect of each other ($p<0.05$) (Table II).

Table-I: Average and standard deviation of hematological parameters in control and experimental groups

Blood parameters	Healthy control (saline)	Doxorubicin	Dox + Crocin	Dox+ training	Dox + training+ Crocin
RBC(10^6/mm^3)	7.58± 0.750	6.24±0.402 *	6.95± 0.645	6.87 ± 0.562	7.17± 0.374
HCT (0/0)	43.46± 4.03	36.43± 3.67*	40.56±3.46	41.33±1.72	42.60±4.82
HGB (gr/dL)	13.72±0.402	10.96±0.564*	11.41±0.563	11.93±0.768	12.56±0.676
PLT (10^3/mm^3)	822±56.51	502±51.95*	685±65.69	600±49.51	781±68.47
WBC (10^6/mm^3)	7.91±0.44	4.27±0.79*	6.07 ±1.28	5.45 ±0.48	6.51 ±0.77
Neutrophil (%)	25.52±3.70	8.80 ±2.15*	15.38 ±1.59	14.13 ±2.73	19.00±1.06
Lymphocyte (%)	72.10±2.88	52.63±4.48	6.07 ±1.28	56.32±7.96	66.16±2.94

* Significant difference between doxorubicin and healthy control groups

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Table-II: Frequency distribution of brain and spinal cord tumors according to studied years

Parameter	Two-way ANOVA test results							
	t test results		Training		Crocin		Interaction	
	t	P values	F	P values	F	P values	F	P values
RBC(10^6/mm^3)	4.366	0.001*	263.255	0.005 #	146.12	0.004#	311.296	0.001#
HCT(٪)	11.788	0.015*	10.287	0.006 #	11.195	0.004 #	14.650	0.001 #
HGB (gr/dL)	9.112	0.001*	20.003	0.012 #	6.342	0.004 #	25.107	0.001 #
PLT(10^3/mm^3)	0.001*	12.574	19.431	0.006#	18.294	0.010 #	28.524	0.002#
WBC (10^6/mm^3)	0.002*	9.081	13.510	0.018 #	11.385	0.004 #	18.244	0.001#
Neutrophil(٪)	8.333	0.002*	19.144	0.005 #	21.548	0.004#	28.436	0.001#
Lymphocyte(٪)	9.377	0.001*	8.259	0.006#	8.382	0.011#	11.253	0.001#

* Denote significant difference between the healthy control group and the doxorubicin group, # Denote significant difference between the doxorubicin group and the recipient groups of the training and supplements

Discussion

In numerous studies, the effects of physical activities on cancer patients have been investigated. One of the problems of cancer patients, especially at the time of receiving chemotherapy drugs, is reduction in the number of blood cell markers, especially red cell count, hematocrit, and hemoglobin levels, which can lead to negative consequences such as anemia, fatigue, depression, decrease physical function, and reduced patient survival (5-9). Researchers have argued that physical activities can increase the levels of blood indexes in inactive people, but the beneficial effect of physical activity, especially high intensity interval training, which has recently been revealed in healthy and patient societies and also in combination with herbal supplements on the blood indexes of cancer patients, has not been reviewed yet. The findings of this study showed that induction of doxorubicin was associated with a significant decrease in all blood indices, so that after 8 weeks of high intensity interval training, the use of crocin and the combination of these two interventions were significantly reversed. In this regard, Dimo et al., studied the effects of aerobic training shortly after discharge from the hospital in patients who received high-dose chemotherapy and bone marrow transplantation. The results of this study showed that the hemoglobin concentration of the participants who participated in the training program increased compared to the untrained patients, which is consistent with the results of the present study. In their study, the inability of the control group during hospitalization was 27% higher than that of the training group and there was a significant difference in maximal physical function in the two groups at the time of discharge. The duration of neutropenia (severe reduction of neutrophil counts) and thrombopenia (reduced platelet count of less than 50,000 per microliter), severity of diarrhea, pain intensity, and duration of hospitalization in the training group decreased significantly (32). Derrine also studied the effects of aerobic training on blood erythrocytes in cancer patients during treatment. The results of this study were expressed in terms of the increase in the number of red cells, hematocrit, and hemoglobin in the experimental group compared to the

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control group, which is consistent with the results of the present study. In the present study, induction of doxorubicin reduced the level of hemoglobin (20%) and red blood cells (18%) in the doxorubicin group compared to the healthy control group. Rezaei Seraji et al. also investigated the effect of aerobic training on blood erythrocyte indices in patients with blood cancers after autologous stem cell transplantation. Their research results showed that the number of red blood cells, hematocrit, and hemoglobin levels decreased after intervention and during discharge from the hospital in both the control and experimental groups, but the decrease in the mean of red blood cells, hematocrit, and hemoglobin in patients in the experimental group was significantly less than the control group, which is consistent with the results of the present study (34). These findings suggest that physical activity may result in the production and release of hematopoietic factors.Chemotherapy reduces blood platelets and, as a result, increases internal bleeding in these patients, which can be one of the causes of anemia. Aerobic activity has been shown to shorten the duration of thrombocytopenia, and possibly aerobic activity helps to improve anemia. The fact that physical activity stimulates the production of erythropoietin is well known. The process of hematopoiesis is a complex process that is affected by several hormones, cytokines, and growth factors. It has been shown that severe and prolonged physical activity, the concentration of several cytokines, and hormones have an effect on the self-division, growthand growth of hematopoietic stem cells. Increased concentration of alpha-necrosis factor, interleukin-β1, interleukin-6, interleukin receptor antagonist, and Granulocyte colony stimulating factor (GCSF) have been observed after severe and prolonged activity (35-38). Physical activity that causes aforementioned changes in the activity of these factors may affect the function of the bone marrow. On the other hand, physical activity reduces some of the pro-inflammatory cytokines in chronic coronary patients. Pro-inflammatory cytokines have a negative effect on iron transfusion and metabolism, resulting in disturbances in hemoglobin synthesis (39). Growth hormone increases significantly in patients with anemia after exercise. This hormone either directly or indirectly (through the insulin-like growth factor) stimulates erythroid and myeloid producer colonies (40). In contrast, Dolen et al., assessed changes in aerobic fitness and hemoglobin levels by investigating patients with breast cancer undergoing chemotherapy. They found that regular aerobic exercise and resistance did not protect patients with breast cancer against the chemotherapy reduction of hemoglobin, but led to a strong link between hemoglobin and maximal oxygen uptake which is not consistent with the results of this study (41). Due to the possible contradiction between the results of these two studies, one can point out the difference in intensity and duration of exercise and the type of subjects. To our knowledge, direct studies have not been conducted on the effects of high intensity interval training or crocin on hematological indices in human and animal models exposed to doxorubicin;however, most studies have been done on the effect of exercise on hematological changes in healthy populations or athletes.

Although white blood cells typically return to baseline hours after intensive exercise in healthy populations, the effect of regular physical activity on cancer patients whose white blood cells are at risk as a result of receiving chemotherapy drugs, has not yet been clearly identified (42). In this regard, Neves et al., showed that severe exercise activities lead to increased leukocytes in healthy men, which leads to leukocytosis (an increase in the number of lymphocytes

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in the tissue), and also the extent of these changes depends on the intensity and duration of exercise; this is consistent with the results of the present study (43). Also, Ajam et al., investigated the effect of 12 weeks aerobic training on some of the immune system and general health indicators of women with breast cancer, revealing that 12 weeks of moderate-intensity aerobic activity (40-60% of maximal beats heart) caused a significant increase in mean white blood cell count in the exercise group and a significant decrease in the control group, which is consistent with the results of the present study (44). In another study on 10 prostate cancer survivors receiving androgen deprivation therapy, Galvao et al., found a significant increase in lymphocytes from baseline after 10 weeks of twice weekly resistance training possibly due to improved immune surveillance in response to resistance training (45). Although more research is needed to substantiate these conclusions, our findings, along with that of past research, suggested positive effect of exercise on WBCs and subsets in cancer patient populations receiving chemotherapy drugs.It has been shown that the destructive effect of doxorubicin on bone marrow is through binding to the DNA strand and inhibiting the production of DNA and RNA, as well as the production of free radicals (46). Therefore, the use of natural and synthetic antioxidants with this drug, as well as the effect of the drug on cancer cells, has always been considered. Saffron and its active ingredients, especially crocin, have anti-genotoxic and antioxidant effects. A comet test on bone marrow in a small mouse showed that saffron administration inhibited chromosomal damage caused by cisplatin, mitomycin, and urea in mice. Crocin has been shown to prevent DNA damage from small mouse bone marrow cells due to the use of anti-tumor drugs called cisplatin, cyclophosphamide, and mitomycin(47-48). Crocin may prevent genotoxic effects of anti-tumor drugs through the effects of lipid peroxidation, antioxidants, and detoxification systems (49). Mohammad et al., showed the therapeutic effect of saffron against the toxicity of doxorubicin in the management of cancer chemotherapy. In their study, 8mg/kg of saffron was used against 5mg/kg doxorubicin in rats. The results showed a significant reduction in the total number of red blood cells, white cells, platelets, and absolute percentages of lymphocytes on the fifth day. When saffron (8mg/kg) was injected five days before doxorubicin injection and continued for 10 days, blood samples were collected for 15 days for histological analysis, a significant increase in the total number of white cells, platelets and absolute lymphocytes were was observed, while no significant differences($P<0.05$) were observed in red blood cells. It seems that flavonoids in saffron, by activating a network of immune responses regulated by T(Th) cells, stimulate B lymphocytes by stimulating the secretion of Th cell cytokines such as IFN-γ to produce IgG Stimulate. Therefore, saffron helps to increase secondary immune responses (IgGs) against doxorubicin poisoning and helps combat the toxic side effects of chemotherapy (50). The main purpose of this study was to investigate the possible effects of high intensity interval training in combination with crocin on blood parameters in rats exposed to doxorubicin. The findings showed that combination of high intensity interval training and crocin prevented severe drop in hematological

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indices. Also, the results showed that intense interval trainings and crocin enhanced the effect of each other so that there was a significant difference between the combined effect of these two interventions and the effect of each of them alone. This finding suggests the use of crocin supplementation along with high intensity interval training, rather than taking each of them aloneto prevent and reduce the complications of treatment with doxorubicin.

Conclusion

According to the results of the current study, performing high intensity aerobic training and crocin consumption as well as a combination of these two interventions can prevent severe drop in hematologic indexes, and improve the treatment and physical function in terms of receiving doxorubicin. It also seems that the combination of training and crocin, compared to the effect of each of the two interventions alone, could more effectively prevent reduction of the hematologic index caused by receiving doxorubicin**.**

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Conflicts of interest

The authors declare no conflict of interest.

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