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The effect of pentoxifylline and different types of exercise training on coagulation factors in a rat endometriosis model

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ABSTRACT

Objectives: This study evaluated the effects of high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), and pentoxifylline (PTX) on coagulation factors, including the amount and percentage of lymphocytes, PLC, PLR, aPTT, PT, PT.I.N. R in a model of rats with endometriosis.
Methods: Endometriosis was surgically induced in female Sprague—Dawley rats. The rats with confirmed endometrial implants were divided into control, MICT, pentoxifylline (D), HIIT+D, and MICT+D, HIIT groups. D and exercise interventions were performed for eight weeks. Then, the macroscopic size of endometriosis lesions was measured, and inflammatory factors (count and percentage of lymphocytes) and coagulation factors, including PLC, PLR, aPTT, PT, PT.I.N. R, and PLR in blood samples were evaluated.
Results: D significantly decreased the volume of lesions and significantly increased PT and PT.I.N. R in blood. HIIT decreased the volume of lesions and significantly increased PT. MICT did not cause significant effects on the target variables. MICT+D decreased the volume of lesions. HIIT+D significantly decreased the volume of lesions and PLC and increased aPTT as well as the count and percentage of lymphocytes, PT, and PT.I.N. R, and decreased PLR.
Conclusions: All interventions(except for MICT) especially HIIT+D and D by priority, induced a significant effect on reducing some indices of inflammation and coagulation.

Introduction

Endometriosis is known as the development of functional endometrial tissue in tissues outside the uterus [1]. It could be a persistent pelvic inflammatory condition that stimulates coagulation pathways and platelets. Thus, women suffering from endometriosis appear to be in a hypercoagulable and hyperinflammatory state [2]. Inflammatory and coagulation mediators may be involved in the growth and progression of endometriosis [1]. Hemostasis balance refers to and relies on various regulated interactions among endothelial blood vessels, platelets, fibrinolysis in the blood, and coagulation proteins [3]. Coagulation factors such as activated partial thromboplastin time (aPTT) and prothrombin time (PT) can disrupt the hemostasis of blood [4,5]. Among the coagulation factors, PT measures the duration of clot formation from the moment of activation of factor VII to the formation of fibrin. aPTT also measures the time required from the activation of factor 12 to the formation of fibrin [6]. Coagulation-related factors such as aPTT, PT, and other coagulator factors are associated with endometriosis [7,8], and aPTT, as well as PT, are shortened in the case of endometriosis [9].

A few blood cells and vessels are changed by inflammation, driving to a prethrombotic condition. In addition to the existence of interference between these two systems, platelet count (PLC) increases in endometriosis patients [9]. The enhancement of the coagulation process in women with endometriosis can be attributed to the idea that endometriotic lesions experience periodical bleeding, causing repetitive tissue damage and repair, which can result in platelet activation and aggregation [2]. Additionally, endometriotic cells reduce platelet-activating molecules, including thrombin and thromboxane A2

Abbreviations: aPTT, Partial thromboplastin time; PT, Prothrombin time; PLC, platelet count; TXA2, thromboxane A2; PTX, Pentoxifylline; MICT, moderate-intensity continuous training; HIIT, high-intensity interval training; D, Drug of PTX; PLR, platelet to lymphocyte ratio; PT.I.N. R, prothrombin time international normalized ratio; TF, tissue factor.

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(TXA2), which is accompanied by increased angiogenesis and permeability of vessels, causing more platelet extravasation or aggregation [10]. Additionally, the blood platelet to lymphocyte ratio (PLR) in women affected by endometriosis increases [11]. In addition, the hypercoagulable state in endometriosis patients has been confirmed by several studies [5, 11, 12]. This condition of hypercoagulation may be accompanied by systemic changes in some inflammatory parameters [9].

Some drug treatments to reduce inflammation may result in unfavorable side effects by suppressing natural platelet function [11]. Some preclinical studies on animals emphasize new treatment methods targeting the hypercoagulative state as a cause of fibrinogenesis and growth of endometriotic lesions [2,13]. Pentoxifylline (PTX), a prevalent treatment method, is an anti-inflammatory and immunomodulatory agent that is recommended for treating endometriosis. Animal studies indicated that PTX significantly suppressed the development of ectopic lesions[14]. PTX alters the transcriptional control of proinflammatory genes [15,16].

Additionally, PTX has antiplatelet and antithrombotic effects [17–19]. In any case, there are some contradictions considering the impact of PTX on endometriosis [20]. Therefore, it appears that other complementary involvements combined with PTX can be supportive in the treatment procedures.

Physical activity has been found to decrease coagulation activity in healthy men and women, as well as in patients due to a decrease in thrombotic risk [21]. Additionally, regular exercise training can suppress the coagulation process [22]. Therefore, physical activity or exercise is suggested as a type of treatment or prevention of endometriosis [23,24], and the reducing effect of various types of exercise on inflammatory factors has been found [24]. Exercise training is performed variously considering mode, duration, frequency, and intensity. To reduce inflammation, several studies recommend moderate-intensity continuous training (MICT) [25]. Previous reports indicate that aPTT can be lengthened after endurance training [26].

A recent finding shows that it is still unclear what type and intensity of exercise can affect fibrinolysis and coagulation [3]. Recently, however, a mode of exercise known as high-intensity interval training (HIIT) has been suggested to reduce inflammatory factors in people affected by metabolic disorders [27]. It appears that HIIT and MICT may result in different impacts on health and physiological responses, but no study was found considering endometriosis patients. The studies conducted on HIIT exercises and their possible effects on the coagulation system of the body are limited; however, contradictory results have been reported even in these limited studies [6]. Therefore, this study aimed to evaluate the influence of the consumption of PTX and performing HIIT and MICT on systemic coagulation levels and inflammation in a model of rats with endometriosis.

Materials and methods

Animals and general procedures

It is a kind of experimental study. Fifty-five female Sprague—Dawley rats (age: 8–9 weeks, weight: 220 ± 20 g) were provided by the Comparative and Experimental Medicine Center in Shiraz. They were kept under normal lighting conditions (12 h light/dark cycle) in a laboratory cage at 25 ± 2 °C. They had free access to water and food (total of 16.6 kJ/g: fat 10.60%, protein 23% and carbohydrate 66.40%).

The normal estrous cycle rats were selected for endometriosis induction by evaluating their daily vaginal smears with a light microscope. Endometriosis was induced by surgery. Six weeks after the initial surgery, endometriosis induction was confirmed by a second-look laparotomy. Eight weeks after the initial surgery, 48 rats in which endometriosis was confirmed were randomly allocated to eight groups: [1] Control: oral gavage of the vehicle (saline) for eight weeks; [2] MICT: executing MICT for 5 days a week; [3] Drug (D) group: gavage of PTX (100 mg/kg/d); [4] MICT+D: executing MICT 5 days a week and gavage of PTX (100 mg/kg/d); [5] HIIT: executing HIIT 5 days a week; [6] HIIT+D: executing HIIT 5 days a week and gavage of PTX (100 mg/kg/d).

Forty-eight hours following interventions, a third laparotomy was performed to assess the effect of involvement on endometriosis lesions, and we sacrificed rats and collected samples for related analysis.

Considering number of groups and the statistical test, the number of animals in each group was estimated as five [28] and for possible reduction of samples, eight rats were assigned to each group. Essentials for the care of laboratory animals defined by the National Institutes of Health, Bethesda, MD, USA, were observed in all the study procedures. The Research Ethics Committee at Shiraz University approved the proposal and procedures of the study (no: IR.US.REC.1401.005).

Induction of endometriosis

Endometriosis was induced through surgery as defined by Vernon and Wilson with some revisions [29]. The rats were anesthetized with 10% ketamine hydrochloride (100 mg/kg, Alfasan, Netherlands) and 2% xylazine (10 mg/kg, Alfasan, Netherlands). Then, abdominal surgery was performed through a midline incision 4 cm to 1 cm below the xiphoid. The left uterine horn was ligated at the ends of the junction of the uterus and cervix and separated. A longitudinal cut was made through the uterine horn. Through perforation biopsy, 4 circular pieces of the distal part of the uterine tissue were separated (5 ×5 mm) and placed in warm sterile saline at 0.9%. The two implants were sutured with proline 5–0 on the left side of the peritoneal cavity above the vascular areas visible with the surface of the endometrium facing the peritoneum. Finally, the muscle groups of the abdomen, fascia, and skin were sutured.

Among 55 rats, three rats died from postoperative hemorrhage. Six weeks following the first surgery, endometriosis induction was confirmed in 48 rats through a second-look laparotomy, and four rats were not diagnosed with any sign of endometriosis.

Pentoxifylline administration

Eight weeks following endometriosis induction, pentoxifylline (Extended Release, Amin Laboratory, Esf, IRAN) was administered to the rats by gavage with 100 mg/kg/d PTX for eight weeks. The doses of the drug were estimated using a formula based on the method of body surface area normalization to determine the dose of drug equivalence between humans and laboratory animals [30]. The weight of the rats was assessed weekly to determine the amount of PTX consumption by the rats according to their weights.

Exercise familiarization and running speed test

Eight weeks after the induction of endometriosis, animals in all groups were familiarized with the environment on the stationary treadmill for three days. Then, for the next five days of familiarization, they ran on the treadmill at a speed of 10 m/min for five minutes.

To determine the speed (intensity) of running in exercise training groups, the animals performed maximum running tests using the maximal incremental running test described by Leit et al. and Rodrigues et al. To execute the test, the rats were initially placed on a stationary treadmill for five minutes. They then ran on a treadmill that was moving at 1 m/min, increasing every six seconds, until they reached 10 m/min on the 10° incline of the treadmill. After that, the timing recording began, and the speed increased by 3 m/min every two minutes until the animals were exhausted and could not continue running [31,32]. The maximum speed at exhaustion was recorded to determine the intensity of the exercise. To determine the speed of running throughout the study, this test was performed at weeks 1, 5, and 8.

Exercise training programs

Forty-eight hours after determining exercise intensity using the maximum running test, the program of exercise training started and was performed according to Table 1. Exercise training included running on a motorized treadmill at 10° of inclination for 8 weeks, 5 days a week. The intensity (speed) of running was determined according to the maximum running test findings and was calculated based on the percentages of the maximum running speed test. Both the HIIT and MICT groups performed 5 min of running on a treadmill for warm-up before the main training program and 5 min of running on a treadmill as cool-down following the main training, both at a speed of 10 m/min.

The MICT included running at 55% of the maximum speed for 31 min during the first week. The intensity increased gradually until the end of the 8th week, reaching 70% of the maximum speed in 46 min. The HIIT program included running sessions for periods of 2 min with a one-minute rest interval. The first week of HIIT included 7 periods of running at an intensity of 85% maximum running, which increased gradually until reaching 12 periods of running at the intensity of 85% maximum intensity, gradually increasing to 12 runs at 85% maximum intensity after eight weeks [31].

Anesthetizing and sampling

Forty-eight hours following the last intervention (drug and exercise training), the rats in all groups were anesthetized with xylazine 2% (10 mg/kg, Alfasan, Netherlands) and ketamine hydrochloride 10% (100 mg/kg, Alfasan, Netherlands) through intramuscular injection. After complete anesthesia of the rat, the abdomen was cut through a midline incision 4 cm from 1 cm below the xiphoid, and endometriotic lesion samples were removed. The width, length, and height of each endometriosis lesion were carefully assessed. The volume was calculated using the ellipsoid volume formula ($\pi/6 \times \text{length} \times \text{width} \times \text{height}$) [33].

Blood sampling and evaluation of blood cells and coagulation factors

Following the treatment, all the rats were anesthetized, blood sampling was performed through cardiac puncture with a syringe, and the samples were poured into anticoagulant blood collection tubes containing liquid sodium nitrate for the following analysis. The count and percentage of lymphocytes (Lym), PLC, and PLR in blood samples were evaluated using a Semi-Automatic Partial diff set (Sysmex KX-21 N hematology analyzer). PLR was attained by dividing the platelet number by the lymphocyte number. PT, aPTT, and PT.I.N. R in blood samples were evaluated by the manual method with a Fisher Kit.

Statistical analysis

SPSS software version 23.0 (SPSS Inc., Chicago, USA) was used for data analysis. The normality of the data distribution was evaluated using the Shapiro—Wilk test. Confirmed normal distribution data were analyzed by one-way analysis of variance (ANOVA). If significant, Tukey HSD or Games-Howell tests were used for pairwise comparisons. For results that were not normally distributed, Kruskal—Wallis H analysis was used to compare the findings between groups. $P < 0.05$ was considered to be statistically significant.

Results

A part of the study findings considered the influence of exercise training as HIIT or MICT and PTX separately or in combination on the lesion size of endometriosis, which was published recently and indicated that administration of D, MICT+D, HIIT, and HIIT+D reduced lesion volume compared with the control group; however, there was no significant difference in lesion volume between groups D, MICT+D, and HIIT. MICT+D, HIIT, HIIT+D, and D significantly reduced lesion volume compared with the MICT group. The volume of lesions in the HIIT+D group was significantly lower than that in all groups, including the control, MICT, D, MICT+D, and HIIT groups[34]. Related figures of lesion volume have been presented in the mentioned reference.

In Fig. 1 macrograph of cysts per rat and in Fig. 2 Specimens of the groups stained by hematoxylin-eosin are shown.

The effect of PTX and exercise training on the counts and percentages of lym, PLC, PLR PT, aPTT, and PT.I.N. R in blood samples: Count and percentage of lym, count of PLC and PT, aPTT, PT.I.N. R, and PLR in blood samples were compared among the six groups in (Fig. 3).

Count and percentage of lym (Fig. 1A, Fig. 1B): The results of the lym count indicated no significant difference between the groups (F=0.861, $p = 0.945$). However, a nonsignificant increase was observed in the number of lym in the HIIT + D ($p = 0.973$), MICT + D ($p = 0.978$), HIIT ($p = 0.998$), and D ($p = 1.000$) groups compared with the control group. However, MICT decreased the lym count compared to the control group ($p = 1.000$).

The results of the percentage of lym showed that there was no significant difference between the groups (F=3.355, $p = 0.196$). A nonsignificant increase was observed in the percentage of lym in the HIIT + D ($p = 0.737$), D ($p = .975$), MICT + D ($p = 0.981$), and HIIT ($p = 0.997$) groups compared with the control group. However, MICT decreased the percentage of lym compared to the control group ($p = 0.796$).

PLC (Fig. 1C): There was a significant difference between groups considering PLC (F=4.212, $p = 0.05$). HIIT+D significantly reduced the PLC count compared to the control group ($p = 0.048$). A nonsignificant decrease was observed in the count of PLC in the MICT ($p = 0.467$), D ($p = 0.509$), HIIT ($p = 0.970$), and MICT + D ($p = 0.991$) groups compared with the control group; however, there was no significant difference in the number of PLCs between the MICT, D, MICT + D, HIIT, and HIIT + D groups ($P > 0.05$).

PLR (Fig. 1D): Considering PLR, there was no significant difference

Table 1
Exercise training protocols for MICT and HIIT.

Training	Measures	W1	W2	W3	W4	W5	W6	W7	W8
MICT	Frequency(days)	5	5	5	5	5	5	5	5
	Inclination(degrees)	10	10	10	10	10	10	10	10
	Velocity(meter/minute)	17	18	20	21	24	27	27	27
	Total duration(minutes)	31	31	37	40	45	46	46	46
	Mode	Continuous and progressive exercise 55–70% max capacity							
HIIT	Frequency(days)	5	5	5	5	5	5	5	5
	Inclination(degrees)	10	10	10	10	10	10	10	10
	Velocity(meter/minute)	24	26	27	30	32	35	38	38
	Total duration(minutes)	31	31	37	40	45	46	46	46
	Periods	7	7	9	10	10	12	12	12
	Mode	Cycles of 2 min exercise + 1 min rest							

W: Week; MICT: moderate-intensity continuous training; HIIT: high-intensity interval training

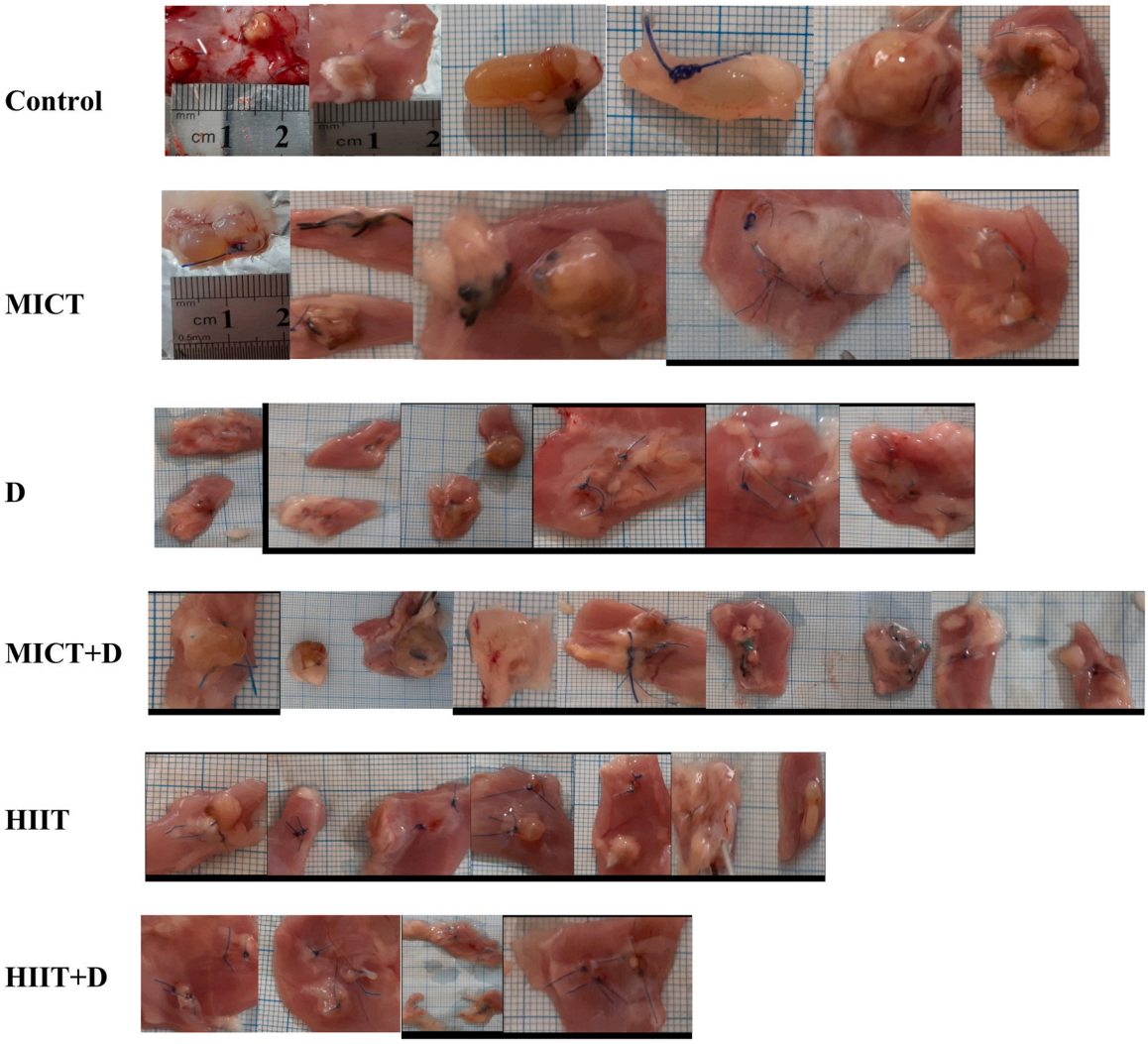

Fig. 1. Macrograph of cysts per rat. D= Drug of pentoxifylline; HIIT= High intensity interval training; MICT= Moderate intensity continuous training; HIIT+D= High intensity interval training + Drug of pentoxifylline; MICT+D= Moderate intensity continuous training + Drug of pentoxifylline.

between the groups (F=1.704, $p = 0.406$). A nonsignificant decrease was observed in the PLR in the HIIT + D ($p = 0.365$), D ($p = 0.774$), MICT ($p = 0.965$), MICT + D ($p = 0.969$), and HIIT ($p = 0.969$) groups compared with the control group.

PT (Fig. 1E): The results showed that there was a significant difference between groups considering PT (F=11.463, $p < 0.001$). Administration of D ($p = 0.001$) and HIIT ($p = 0.049$) significantly increased PT compared with the control group. A nonsignificant increase was observed in PT in the MICT + D ($p = 0.087$) and HIIT + D ($p = 0.853$) groups compared to the control group, but MICT ($p = 0.999$) decreased PT compared with the control group. D ($p < 0.001$), HIIT ($p = 0.022$), and MICT+D ($p = 0.043$) significantly increased PT compared with the MICT group.

aPTT (Fig. 1F): The results showed that there was a significant difference between groups considering aPTT (F=16.350, $p = 0.04$). Only HIIT+D significantly increased aPTT compared with the control group ($p = 0.014$). A nonsignificant increase was observed in aPTT in the HIIT ($p = 0.133$), MICT + D ($p = 0.134$), and D ($p = 0.204$) groups compared with the control group. Administration of MICT ($p = 0.687$) decreased aPTT compared with the control group. In addition to HIIT+D ($p = 0.006$), HIIT ($p = 0.024$), MICT+D ($p = 0.026$), and D ($p = 0.043$) significantly increased aPTT compared with the MICT group. There was no significant difference in aPTT between the D, MICT + D, HIIT, and HIIT + D groups ($P > 0.05$).

PT.I.N. R (Fig. 1G): The results showed that there was a significant difference between the groups regarding PT.I.N. R (F=11.016, $p < 0.001$). Only the administration of D increased PT.I.N. R compared to the control group ($p = 0.001$). A nonsignificant increase was observed in PT.I.N. R in the MICT + D ($p = 0.105$), HIIT ($p = 0.154$), and HIIT+D ($p = 0.860$) groups compared to the control group. MICT decreased PT.I.N. R compared to the control group ($p = 1.000$). Administration of D increased PT.I.N. R compared with the MICT group significantly ($p < 0.001$), and MICT+D ($p = 0.059$), HIIT ($p = 0.087$), and HIIT+D ($p = 0.728$) increased PT.I.N. R compared with the MICT group nonsignificantly. There was no significant difference in PT.I.N. R between the D, MICT + D, HIIT, and HIIT + D groups ($P > 0.05$).

Discussion

Platelet activation and the coagulation cascade raise extreme concern that the risk of thromboembolism may be increased in patients with endometriosis. It appears that coagulation factors in peripheral blood and hypercoagulable status can be important in the progression of the disease[2]. This is the first study to evaluate the effects of PTX with MICT and HIIT, separately or in combination, on anti-inflammatory and anti-coagulation factors in endometriosis. Our results indicated that the endometriosis lesion volume in the control group was greater than that in the other groups, whereas the control group had higher blood

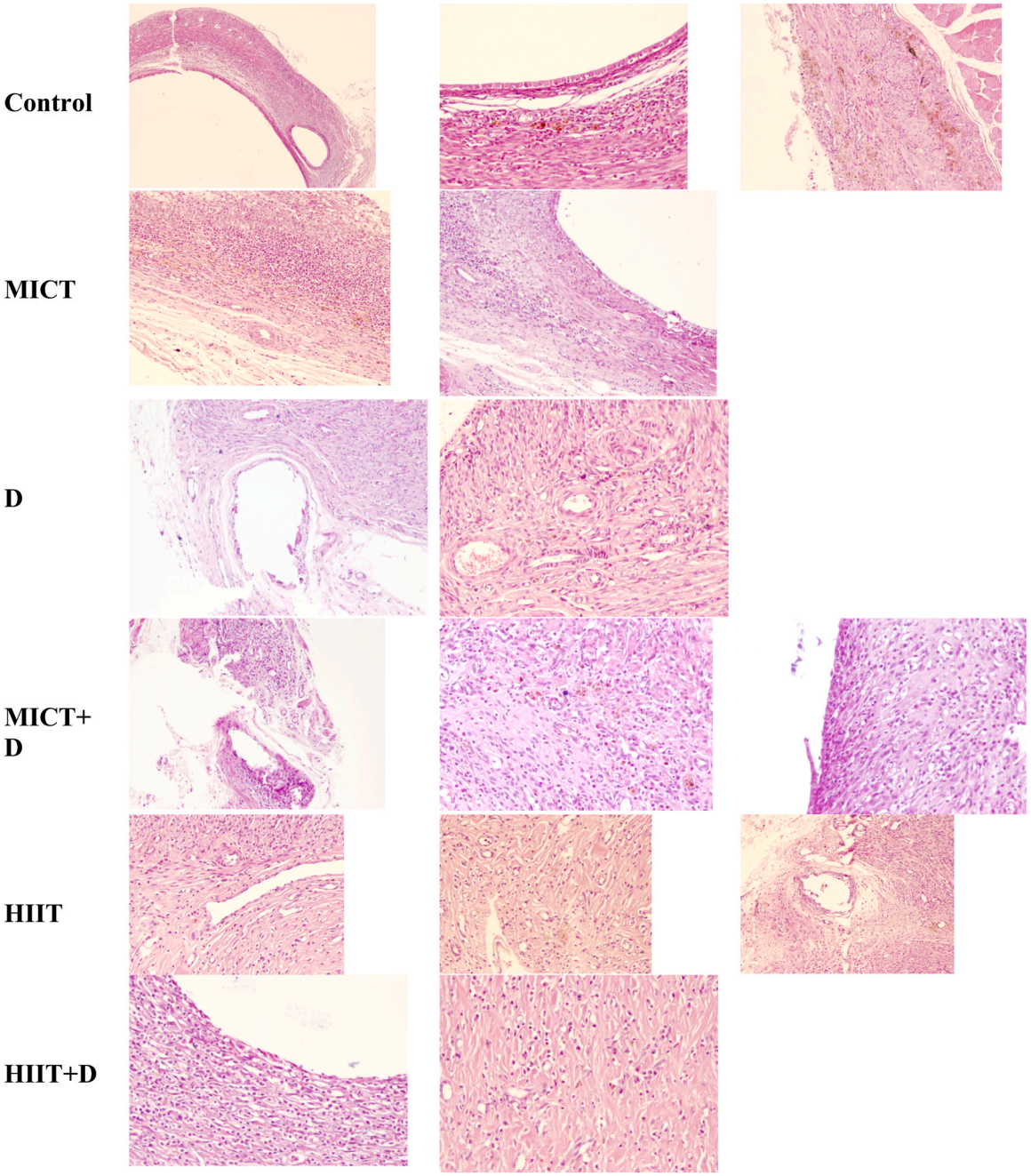

Fig. 2. Specimens of the groups stained by hematoxylin-eosin. D= Drug of pentoxifylline; HIIT= High Intensity Interval Training; MICT= Moderate Intensity Continuous training; HIIT+D= High Intensity Interval Training + Drug of pentoxifylline; MICT+D= Moderate Intensity Continuous training + Drug of pentoxifylline.

inflammation and coagulation status. There is growing evidence that a high interaction exists between the systems of coagulation and inflammation, whereas inflammation causes the activation of coagulation, which significantly affects inflammatory activities[35]. In our study, the amount and percentage of lymphocytes, PT, PT.I.N. R, and aPTT in the control group, as endometriosis rats that did not receive any therapeutic intervention, were lower than those in other groups (except for the MICT), while PLC and PLR were higher in the control group than those in other intervention groups. These results demonstrate the negative impact of endometriosis on the inflammatory and coagulation systems. Previous evidence reported higher coagulation status in endometriosis and other diseases, which is similar to the present study findings [1, 8, 9, 36]. Therefore, it appears that therapeutic interventions that modulate these coagulation factors and their dependent pathways can improve endometriosis. Our unreported findings indicated that aPTT, PT, and PT. I.N. R were negatively correlated with the mean lesion size, while PLC and PLR were positively correlated with it. Additionally, another study found that aPTT and PT were negatively correlated with mean cyst diameter[8].

Some findings indicate that inflammation stimulates the coagulation cascade in reaction to TF-mediated thrombin generation[1]. Tissue factor (TF) plays an important role in initiating inflammatory coagulation when exposed to blood, triggering a cascade of reactions that culminate in the generation of thrombin[35]. TF attaches to circulating factor VIIa to mediate the activation of factors IX and X and produces thrombin[1]. TF might combine with the circulating factor of VII-a to contribute to the exogenous coagulation pathway[12]. Endometriotic lesions can influence this reaction[9]. Therefore, one of the reasons for

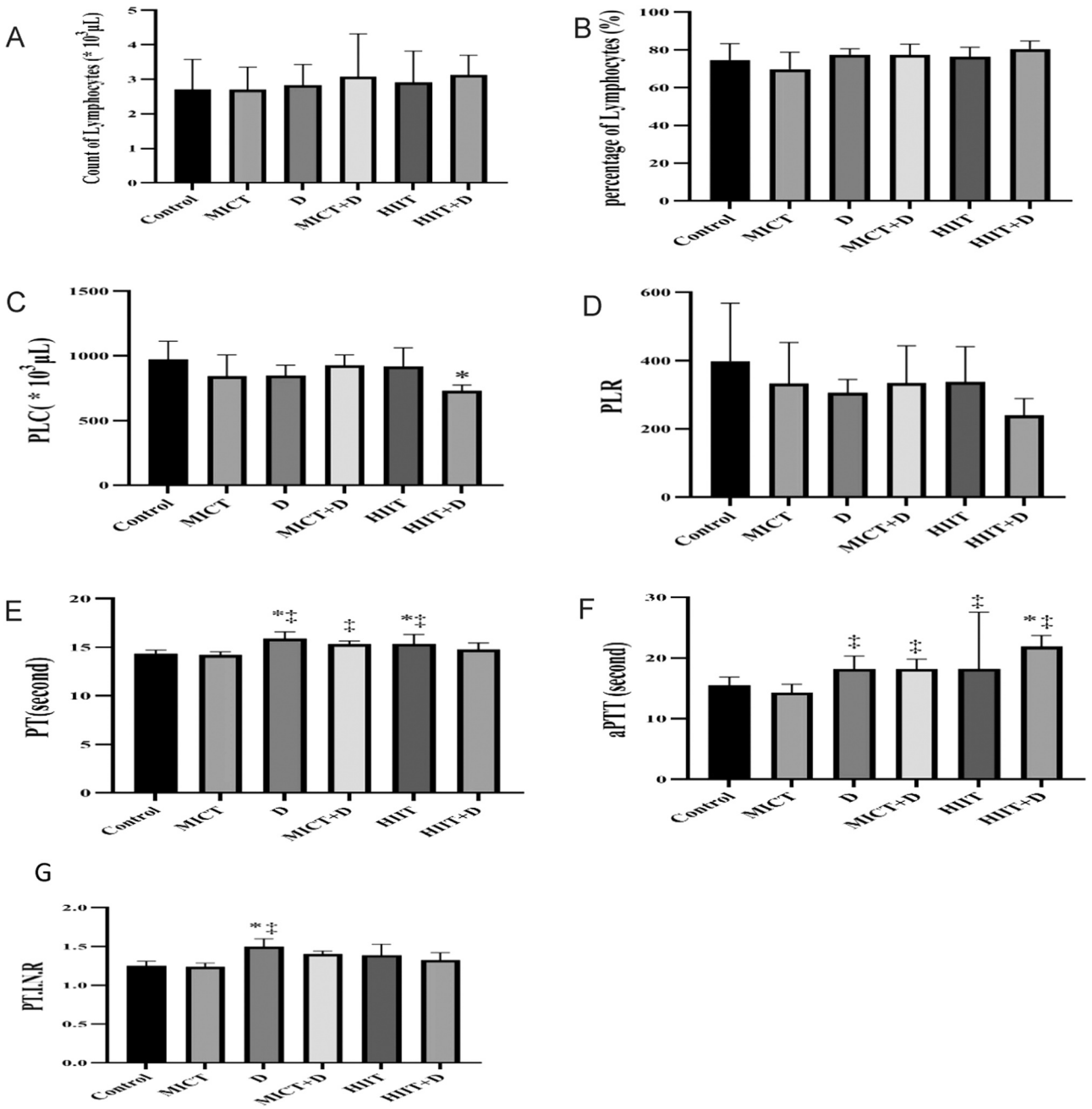

Fig. 3. Manual Assay of PT, aPTT, PT.I.N.R, and Semi-Automatic Assay of the count of lym, percentage of lym, PLC, and PLR in blood samples. (A) comparison of lym (lymphocytes), (B) the percentage of lym (lymphocytes), (C) PLC (platelets), (D) PLR (platelet to lymphocytes ratio), (E) PT (Prothrombin time), (F) aPTT (activated Partial thromboplastin time),(G) PT.I.N.R (Prothrombin time International Normalizes ratio) between different groups. D= Drug of pentoxifylline; HIIT= High Intensity Interval Training; MICT= Moderate Intensity Continuous training; HIIT+D= High Intensity Interval Training + Drug of pentoxifylline; MICT+D= Moderate Intensity Continuous training + Drug of pentoxifylline. $p \leq 0.05$ was considered significant: * significant difference compared to. control group; ‡ significant difference compared to MICT group.

the increase in coagulation factors in the rat model of endometriosis in our study could be the expression of TF in endometriotic lesions. In addition, protease-activated receptor 2 (PAR-2), activated by TF/FVIIa, is upregulated in the glandular epithelium of the eutopic endometrium. TFs and PAR-2 receptors are mediators of angiogenic and inflammatory signaling in endometriotic lesions. Shorter aPTT correlates with higher levels of coagulation factors and factors related to increased thrombin generation in plasma[9]. Periodic bleeding from endometriotic lesions affects the local release of factors, including thrombin, activating platelets (PAFs), and thromboxane A2 (TXA2), which result in enhanced angiogenesis and vessel permeability and cause platelet activation and aggregation[9,10]. Activated platelets can increase the release of von Willebrand factor (vWF), PAF, TXA2, adenosine diphosphate (ADP), serotonin, and chemokine (C-X-C motif) ligand 4 (CXCL4), resulting in higher platelet aggregation and maintaining coagulation activation [37]. In particular, platelet extravasation and aggregation may eventually cause fibrosis in endometriosis lesions [9,37]. Therefore, the mentioned mechanisms can be the cause of the increased accumulation of platelets, PLC, and PLR in the blood of rats with endometriosis in our study.

Modulation of the mentioned coagulation pathways in endometriosis can produce an important treatment method. Interestingly, Ding et al.

[9] and Wu et al. [2] showed that following surgery for endometriotic lesion elimination, the coagulation factors and extent of platelet activation in the peripheral blood were reduced significantly, which is probably the result of the reduction or inhibition of endometriotic foci, which are activators of platelet activation.

PTX, a nonspecific phosphodiesterase (PDE) inhibitor, is commonly utilized to improve the rheological properties of blood [38]. PTX suppresses adenosine-induced platelet aggregation [17,39]. PTX suppresses the activation of platelets by increasing prostacyclin and cAMP[17]. Studies confirm the important antithrombotic impact of PTX through modulation of the coagulation cascade and suppression of platelet aggregation. Additionally, PTX reduces platelet activation[17,40]. Thus, these effects could help to prevent or mitigate the inflammatory response and hypercoagulability that develop with endometriosis. The results of our study indicated that the group consuming PTX for eight weeks showed a decrease in PLC and PLR compared to the control group, which indicates the effect of PTX in reducing coagulation conditions, although this reduction was not statistically significant. Considering that PTX can be used for a long time, a longer use of this drug may cause more significant results. Our result regarding PLC is in line with previous evidence demonstrating that PTX can reduce coagulopathy in COVID-19 by increasing the inhibition of platelet aggregation [17]. In addition, the results of our study showed that PTX caused a nonsignificant increase in the number and percentage of lymphocytes and aPTT, but PTX significantly increased PT and PT.I.N.R. Therefore, PTX, with its antithrombotic, anticoagulant and anti-inflammatory potential, was able to modulate coagulation pathways and reduce inflammatory and coagulation factors in our study. Although the positive effect of PTX on the treatment of endometriosis has been confirmed, a recent review [20] indicated controversies regarding the influence of PTX on endometriosis and its related symptoms. Therefore, it appears that complementary involvement combined with PTX consumption can enhance the impacts of this drug. In the present study, for the first time, HIIT and MICT, as two types of common exercise training, were used as complementary interventions, and their anti-inflammatory impacts are well known. Additionally, it has been shown that regular exercise training leads to a decrease in procoagulant activity [41], which induces a great effect on the physiology of blood coagulation [42] and may positively influence the hemostatic system by regulating fibrinolytic and coagulation blood profiles [43]. The findings have indicated that regular aerobic exercise significantly regulates homeostasis by reducing precoagulation factors and increasing anticoagulation factors [44,45]. Possible related mechanisms are that aerobic exercise enhances vascular endothelial integrity, vascular permeability, and the release of vasodilators [46], such as nitric oxide, which induces the release of tissue plasminogen activator (tPA) from endothelial cells [46,47] and suppresses plasminogen activator inhibitor type 1 (PAI-1) production by vessels and platelets [46]. An inverse correlation has been shown between physical activity and TF (factor VIII) [48,49], and factor VII decreases in sedentary men following three months of aerobic exercise training [48]. However, another study found no relationship between physical activity and factor VII or factor VIII concentrations [48] and indicated that the extrinsic, or 'TF' pathway, does not significantly affect exercise-induced changes in coagulation activity[26]. The effect of training on the hemostasis system is dependent on some factors, including type, intensity, duration, and training condition [50]. Generally, there is inadequate information regarding the effect of exercise training on coagulation factors, and considering these variables in future studies is needed.

The fluctuations in PT duration (time to clot formation) may be influenced by the type of exercise training, as PT decreases with increasing exercise duration [5]. Therefore, this could be the reason for the reduction in PT in the MICT group in our study, which was even lower than that in the control group. Piccione et al. reported an increase in PT after short-term aerobic exercise. According to Piccione et al., the difference in the response to exercise in different studies confirms that the type of exercise training (along with the age, gender, and initial condition of the subjects) has a significant effect on the response of the coagulation system [51,52]. Other researchers have explained that MICT had a significant reducing effect on PAI-1 [53]. A significant increasing effect of exercise training on clotting time has also been observed [53]. Gram et al. [54] showed that MICT in overweight adults reduced the probability of cardiovascular disease and regulated hematological indices by decreasing blood coagulation factors [44]. However, our results showed that MICT does not induce any positive effect on the coagulation system in endometriosis. The decrease in PT.I.N. R and aPTT in the MICT group may be related to the intensity, duration, and mode of training. The duration and mode of exercise training affect coagulation and fibrinolytic factors, which may alter blood hemostasis. These changes can cause a faster blood clotting time, which is serious for patients with cardiovascular disease [5]. The findings of the present study are in agreement with the findings of Womack [49] and Hilberg and Menzel [6], which demonstrated a shortening of aPTT after MICT in young men and older adults following exercise training. Additionally, in another study, a reduction in aPTT by implementing different exercise training protocols in people was found [52]. aPTT is greatly affected by VIII factors [52] as an indicator of the intrinsic pathway activation potential [55]. The reduction in aPTT in the MICT group was probably accompanied by elevated levels of factor VIII antigen (FVIII: Ag).

Recent reports showed that endurance exercise with moderate intensity did not activate the coagulation system, while very high-intensity endurance exercise was related to the activation of this system [6,56]. The findings of previous studies demonstrated that high-intensity exercise can increase TF (FVIII) and decrease aPTT and PT, causing hypercoagulable conditions, which may be due to an increased blood lactate concentration, PLC, and catecholamine levels [50,57]. This could be the result of the response of the coagulation system to a session of intense activity, but in our study, the adaptation of the coagulation system was investigated after eight weeks of HIIT and showed the amount and percentage of lymphocytes, aPTT, PT, PT.I.N. R increased and PLC and PLR decreased. Regular exercise appears to reduce the adverse effects of exercise on hematological and coagulation indices [42]. Exercise intensity has a greater effect on blood clotting and fibrinolysis than exercise duration [5]. Thus, it appears that the increase in fibrinolysis following HIIT can be one of the reasons for the increase in anti-coagulant conditions in the homeostasis system in our study. The results of the present study are consistent with the findings of Sobhani et al. [58]. They observed that PT in high-intensity exercise increased significantly. Considering that prothrombin, as an important protein in the coagulation process, is continuously produced by the liver, perhaps the reduction of hepatic blood flow is effective in its production [52]. Hence, the longer PT in the HIIT group in the present study may be due to the reduction in homeostasis factors due to the reduction in hepatic blood flow. Contrary to these results, a recent study does not advocate the theory that a higher exercise intensity induces adaptation as measured by PT. Eight weeks of HIIT has not been shown to affect blood clotting and/or induce fibrinolysis. Although previous results show that fluctuations in blood clotting and fibrinolysis may be related to exercise intensity [26], their findings do not support this claim [26].

Jacobina Kristiansen et al. found that regular high-intensity exercise training did not influence thrombin generation, platelet aggregation, or fibrinolysis in patients [59]. Some recent studies demonstrated that compared with MICT alone, HIIT in combination with MICT caused a decrease in the platelet response, with no significant effect on platelet activation [59,60].

Additionally, according to the present findings, aPTT, PT, and PT.I.N. R increased after HIIT+D and MICT+D, but only HIIT+D and HIIT significantly increased aPTT and PT, respectively. These findings indicate that regular HIIT alone and in combination with PTX can be effective in improving the coagulation status of endometriosis and ultimately lead to endometriosis improvement. Furthermore, HIIT and PTX alone and in combination with each other (HIIT+D) and PTX alone and in combination with MICT (MICT+D) had a positive effect on the

amount and percentage of lymphocytes and probably had a positive effect on the coagulation system through the improvement of the inflammatory condition.

The results of our study showed that HIIT and MICT separately and combined with PTX decreased the PLC and PLR, and only HIIT+PTX caused a significant decrease in PLC. These results indicate that HIIT, by enhancing the anticoagulant effect of PTX, caused a significant reduction in PLC and improved coagulation. Platelets play a crucial role in hemostasis. Based on available studies [59,60], it can be hypothesized that regular physical exercise could cause a decrease in platelet aggregation and turnover. The probable mechanism for platelet depletion in all exercise groups in the present study could be related to increased epinephrine secretion, resulting in the elimination of all ions from substances[44]. The main mechanism of platelet depletion following aerobic exercise may be due to an increase or maintenance of blood pH as a result of adaptation to exercise[44]. However, another study did not show any changes in platelets after 12 weeks of exercise training[59]. On the other hand, most studies show an increase in platelet number following exercise training [44], which is not consistent with the findings of the present study. An increased platelet number seems to be related to blood return from the spinal cord and bone marrow, as well as the accumulation of blood in the vessels from the lungs to the muscles [44]. The difference between most training programs in other studies and the current study is the training intensity. In the mentioned studies, the training intensity was higher than that in our study.

These conflicting results support the idea that the influence of exercise training on the coagulation system is correlated with the exercise mode, duration, and intensity as well as types of medical conditions[36]. Also, there may be an overlap between genotype and phenotypic characteristics so that genetic causes somatic traits which may introduce new pathways in the molecular aspects of endometriosis [61–63] and may cause even different adaptations or responses to exercise training. Not considering genetic aspects is a limitation of this study and is recommended for future studies. Also, reproductive dysfunction and endometriosis can be linked to important mediating factors of leptin[64,65], hypothalamic-pituitary-gonadal hormonal pathways (HPA), kisspeptin [66], insulin and insulin like growth factor-1(IGF-1)[67] which can be affected differently by various exercise; not measuring them were other limitations of this study and are recommended to be considered in future studies.

Altogether, our study demonstrated that MICT alone did not affect coagulation in endometriosis and that MICT did not improve the endometriosis condition. However, HIIT and PTX alone and in combination induced anti-inflammatory and positive effects on the coagulation pathways and improved endometriosis. It can also be concluded that HIIT induced a synergistic effect when combined with PTX. The detected improvement in coagulation status may be a mechanism by which PTX and HIIT alone and in combination can reduce the thrombotic and cardiovascular risks in endometriosis conditions.

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CRediT authorship contribution statement

Maryam Koushkie Jahromi: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing. **Zahra Salehpoor:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Project administration, Software. **Mohamad Rezapourmoghadam:** Data curation, Investigation. **Nader Tanideh:** Conceptualization, Data curation, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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