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Selenium Effect on Ischemia-Reperfusion Injury of Gastrocnemius Muscle in Adult Rats

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Abstract Selenium is a trace element that has antioxidant and neuroprotective effects. The aim of this study is to investigate the effects of selenium in reducing ischemia-reperfusion injury of the gastrocnemius muscle. In this experimental study, 80 adult male Wistar rats weighing 250–300 g were divided into ten groups (N=8 per group). Group 1 is control group (without ischemia-reperfusion). Group 2 received 0.2 mg/kg selenium. Group 3 received ischemia+3 d reperfusion+0.2 mg/kg selenium, group 4 received ischemia+3 d reperfusion+0.2 mg/kg placebo, group 5 received ischemia+7 d reperfusion+0.2 mg/kg selenium, group 6 received ischemia+7 d reperfusion+0.2 mg/kg placebo, group 7 received ischemia+14 d reperfusion+0.2 mg/kg selenium, group 8 received ischemia+14 d reperfusion+0.2 mg/kg placebo, group 9 received ischemia+28 d reperfusion+0.2 mg/kg selenium and group 10 received ischemia+3 d reperfusion+0.2 mg/kg placebo. External iliac artery blocked for 3 h. After reperfusion, rats killed and gastrocnemius muscle removed, fixed, and tissue processing performed. Samples stained with hematoxylin-eosin for edema evaluation, toluidine blue for mast cell infiltration evaluation and immunohistochemistry for detection TNF-alpha and NF-kappa B proteins. Comparison of mast cell infiltration, edema of the interstitial fluid on the tissue, expression of TNF-alpha protein, and expression of NF-kappa B protein in the groups that received selenium with corresponding placebo group showed that selenium can reduce edema, mast cell infiltration, and TNF-alpha expression and inactivated NF-kappa B. The use of selenium simultaneously with creating ischemia can reduce ischemia-reperfusion injury of the gastrocnemius muscle.

Keywords Ischemia-reperfusion · Muscle · TNF-alpha · NF-kappa B

Introduction

Ischemia is one of the most common injuries that are usually caused by decreased blood flow and consequent lack of oxygen and nutrients, and energy production stopping that occurs in vascular substrates of the tissues [1]. Ischemia-reperfusion in skeletal muscles begins by a series of cellular and systemic events. During ischemia, there is a gradual decrease in intracellular energy storage. However, reperfusion causes harmful effects, such as excision of required precursors for the adenine nucleotide synthesis. Production of free radicals and lipid peroxidation and oxidative phosphorylation and disruption of calcium diffusion occurs in mitochondria. Neutrophils and endothelial leukocytes lead to prolongation of reperfusion injury [2]. It is clear that skeletal muscles are more exposed to ischemia than other tissues. Damage to muscles is the most critical aspect of reperfusion in the limbs. The degree of skeletal muscle damage is directly related to the severity and duration of ischemia. Accurate determination of the time of muscle death is difficult because the microscopic and macroscopic changes are very small. Researcher showed that 3 h ischemia in the muscle rat led to significant muscle damage. The injury was very severe after 4, 5 and 6 h ischemia that these led to 3 % loss of functional activity control [3].The pathophysiologic and clinical aspects of skeletal muscle ischemia-reperfusion have been studied significantly. Reactive oxygen species (ROS) and nitrogen (NOS) have been implicated in

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tissue damage induced by ischemia-reperfusion. The reactive species that are derived from various sources such as the mitochondrial electron transport chain, oxidized xanthine-xanthine reaction, may be very early in the injury of ischemia-reperfusion [4–6]. Ischemia-reperfusion injury in skeletal muscle can be seen in trauma, bed sores, infections, and surgical mistakes. Ischemia-reperfusion in skeletal muscle samples cause metabolic stress reduction that this leads to energy reduction and cell edema and eventually cause tissue damage and organ dysfunction. Reperfusion paradoxically initiates a stream of events that may cause further damage to cell [7]. One proposal to reduce ischemia-reperfusion injury is the simultaneous use of antioxidants. Selenium is one of the antioxidants that recently the interest of researchers. Selenium, a trace element, has an antioxidant and neuroprotective effect for the biological function of scavenging oxygen free radical [8]. Selenium protects DNA, lipids, and proteins against free radical [8]. Selenium reduces hydroperoxidize and lipoperoxidizes through an activity similar to glutathione peroxidase [8]. The protective effect of selenium has been shown in several studies against ischemia-reperfusion [8, 9]. Researchers showed selenium may have beneficial effect on prefrontal cortex and hippocampus [8]. Studies conducted in countries with a low intake of the selenium in the diet was shown that plasma selenium levels less than 45 μg/L is associated with an increased risk of heart disease. Giving selenium supplements to populations in areas where endemic selenium deficiency and cardiomyopathy reduce Cushing's disease [9]. Multiple pre-clinical studies showed that myocardial ischemia-reperfusion injury is reduced by the selenoprotein and mainly by glutathione peroxidase. Studies showed that high levels of selenium cause to increase of immature collagen in various organs including the heart [9]. According to the positive effects of selenium in reducing ischemia-reperfusion injury in various tissues, this antioxidant can be effective to reduce ischemia-reperfusion injury of skeletal muscles. The main goal of the present study was to examine selenium effects on ischemia-reperfusion injury of gastrocnemius muscle.

Materials and Methods

This is an experimental study that was performed at Razi herbal medicine research center of Lorestan University of Medical Sciences. All animals were obtained from Razi Herbal Medicine Center of Lorestan University of Medical Sciences. Every effort was made to minimize the number of animals used and their suffering. In this experimental study, 80 adult male Wistar rats weighing 250–300 g were used that were divided into ten groups (N=8 per group). The animals were acclimatized for 1 week to the condition of our laboratory before the commencement of the experiment. The animals were exposed to 12 h light and 12 h dark cycle at a room temperature of 22 °C. The animals had free access to standard laboratory chow and water ad libitum. The studies were performed during the same time in all groups. The rats were grouped as follows

Group 1: control group (without ischemia-reperfusion)
Group 2: only received 0.2 mg/kg of selenium (in order to assess the possible deleterious effects) without ischemia-reperfusion
Group 3: 3 h of ischemia and 3 d reperfusion with0.2 mg/kg injection of selenium
Group 4: 3 h of ischemia and 3 d reperfusion without injection of selenium
Group 5: 3 h of ischemia and 7 d reperfusion with 0.2 mg/kg injection of selenium
Group 6: 3 h of ischemia and 7 d reperfusion without injection of selenium
Group 7: 3 h of ischemia and 14 d reperfusion with 0.2 mg/kg injection of selenium
Group 8: 3 h of ischemia and 14 d reperfusion without injection of selenium
Group 9: 3 h of ischemia and 28 d reperfusion with 0.2 mg/kg injection of selenium
Group 10: 3 h of ischemia and 28 d reperfusion without injection of selenium

Groups 3, 5, 7, and 9 above are known as placebo groups and were injected normal saline (selenium solvent) instead of selenium. The rats were anesthetized once intraperitoneally (IP) with ketamine HCl (50 mg/kg) and xylazine (5 mg/kg) [10] in accordance with the protocol approved by the Animal Care and Use Committee and prepared for surgery. To create ischemia, the inguinal area has been shaved and after disinfection; the femoral artery and vein were carefully separated from the femoral nerve with an inguinal incision, and then the artery and vein were knit using a silk suture 6/0 [11] and slipknot technique [11] for 3 h. Tissue perfusion was performed after 3 h based on above mentioned various times of reperfusion. Normal saline and selenium (respectively in experimental and placebo groups), both coinciding with ischemia were injected IP. The rats killed at required time with a high dose of anesthetic and gastrocnemius muscle removed and fixed in 10 % formalin.

Histopathological Studies

Gastrocnemius muscle after fixation, embedded in paraffin, cutting and dehydration stained with hematoxylin-eosin and toluidine blue staining for analysis edema and fiber degeneration and mast cell infiltration, respectively. Analysis of 30 randomly selected fields per slide performed with light microscope (magnification of 40). Disorganization and degeneration of muscle fibers, infiltration of inflammatory cells, and

Table 1 Mast cell infiltration compared at different times of ischemia-reperfusion with and without injection of selenium which each group compared with placebo using Mann-Whitney *U* test

Groups of study	Mast cell infiltration		*P* value
	Mean of ranks	Mean±SD	
3-d reperfusion without selenium injection (group 4)	12.44	3.25±0.88	<0.001
3-d reperfusion with selenium injection (group 3)	4.56	0.63±0.7	
7-d reperfusion without selenium injection (group 6)	12	5.13±1.5	0.002
7-d reperfusion with selenium injection (group 5)	5	2.63±1.1	
14-d reperfusion without selenium injection (group 8)	8.81	4.13±1.8	0.79
14-d reperfusion with selenium injection (group 7)	8.19	3.63±1.2	
28-d reperfusion without selenium injection (group 10)	9.25	4.25±0.7	0.57
28-d reperfusion with selenium injection (group 9)	7.75	4±0.75	

edema of the interstitial fluid on the tissue performed as follows: 0, normal; 1, mild; 2, moderate; 3, severe (7).

Immunohistochemical Studies

TNF-alpha

Immunohistochemical staining was performed according to the method of AbD Serotec company procedure with slight modifications [12]. After fixation, embedded in paraffin and cutting, paraffin was removed from the specimens by Xylene and specimens were dehydrated in ethanol. Antigens retrieval was done in citrate buffer (pH=6) for 15 min at 98 °C. Samples were incubated with 0.3 % (*w*/*v*) H2O2 in PBS for 15 min to block endogenous peroxidase activity. Wash three times in PBS. Samples were incubated with 10 % normal goat serum (Cell signaling, #5425) for 10 min. The samples were incubated overnight with primary antibody (rat anti-mouse TNF-alpha, AbD Serotec, # MCA 1488). Primary antibodies were diluted in PBS at the ratio of 1:100. At this stage, PBS only was added to the negative control samples. Samples were incubated 30 min with one drop secondary antibody (Rabbit F (ab´) 2 anti-rat IgG: HRP, AbD Serotec, # STAR21B). After washing, samples were incubated with one drop SignalStain® DAB Substrate Kit (Cell signaling, #8059) that was diluted with 1 ml HRP-Stabilizing Diluent (AbD Serotec, #BUF052C). After wahing with PBS, samples were counterstained with hematoxylin counterstain for 1 min and then washed. Samples dehydrate through a graded series of alcohols, xylene, and mount in aqueous mounting medium. The results were analyzed by specialists that were blinded to the study. Analysis of 30 randomly selected fields per slide performed with light microscope (×40 magnification).

NF-kappa B

Immunohistochemical staining was performed according to the method of cell signal company procedure with slight modifications [12]. After fixation, embedded in paraffin and cutting, paraffin was removed from the specimens by Xylene and specimens were dehydrated in ethanol. Antigens retrieval was done in citrate buffer (pH=6) for 15 min at 98 °C. Samples were incubated with 3 % (*w*/*v*) H2O2 in PBS for 15 min to block endogenous peroxidase activity. Wash three times in PBS. Samples were incubated with 10 % normal goat serum (Cell signaling, #5425) for 10 min. The samples were incubated overnight with primary antibody (Rabbit anti NF-Kb p65 (D14E12) XP® Rabbit mAb, Cell signaling, #8242). Primary antibodies were diluted in PBS at the ratio of 1:100. At

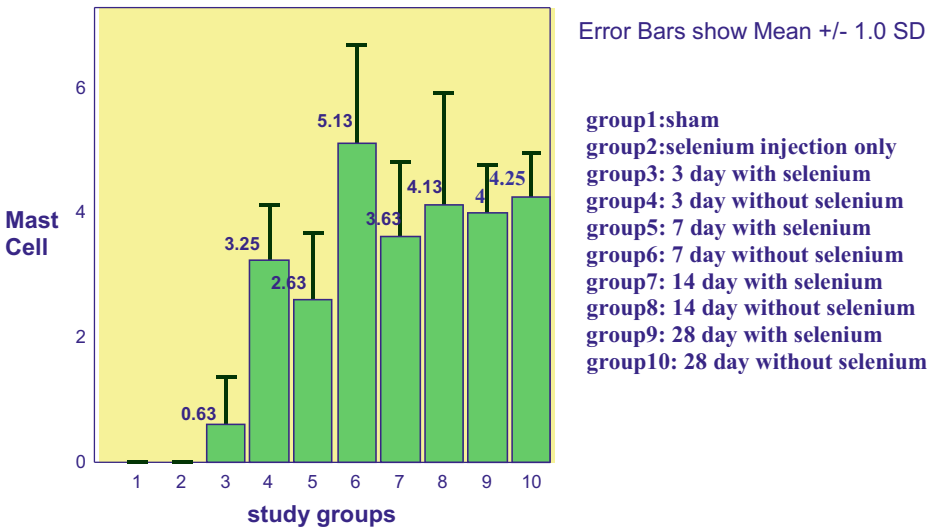

Fig. 1 Mast cell infiltration in groups of study

Table 2 Edema of the interstitial fluid on the tissue compared at different times of ischemia-reperfusion with and without injection of selenium which each group compared with placebo using Mann-Whitney *U* test

Groups of study	Edema of the interstitial fluid on the tissue		*P* value
	Mean of ranks	Mean±SD	
3-d reperfusion without selenium injection (group 4)	12.5	3.25±0.46	<0.001
3-d reperfusion with selenium injection (group 3)	4.5	1±0.92	
7-d reperfusion without selenium injection (group 6)	12.38	3.75±3.2	<0.001
7-d reperfusion with selenium injection (group 5)	4.63	1.13±1.12	
14-d reperfusion without selenium injection (group 8)	11	3.38±0.91	0.038
14-d reperfusion with selenium injection (group 7)	6	2.25±0.88	
28-d reperfusion without selenium injection (group 10)	11.31	4±0.53	0.015
28-d reperfusion with selenium injection (group 9)	5.69	2.88±0.83	

this stage, PBS only was added to the negative control samples. Samples were incubated 30 min with one drop secondary antibody (SignalStain® Boost IHC Detection, Cell signaling, #9997). After washing, samples were incubated with one drop SignalStain® DAB Substrate Kit (Cell signaling, #8059) that was diluted with 1 ml HRP-Stabilizing Diluent (AbD Serotec, #BUF052C). After washing in PBS, samples were counterstained with hematoxylin counterstain for 1 min then wash. Samples dehydrate through a graded series of alcohols, xylene, and mount in aqueous mounting medium. The results were analyzed by specialists that blind to study. Analysis of 30 randomly selected fields per slide performed with light microscope (×40 magnification).

The Statistical Analysis

Mann-Whitney *U* test and Dunn's multiple comparison tests were chosen for analysis variables (SPSS-22). Results are presented as means±SD. Results considered significant at $p \leq 0.05$.

Results

Comparison of mast cell infiltration between groups selenium treated with the placebo corresponding groups suggests that difference between group 3, 3 d reperfusion with selenium injection, and group 4, 3 d reperfusion without selenium injection (*p* value=*<0.001*, Table 1, Fig. 1) are statistically significant and comparison between group 5, 7 d reperfusion with selenium injection, and group 6, 7 d reperfusion without selenium injection (*p* value=*0.002*, Table 1, Fig. 1) are statistically significant.

Comparison of edema of the interstitial fluid on the tissue between groups selenium treated with the placebo corresponding groups suggests that difference between group 3, 3 d reperfusion with selenium injection, and group 4, 3 d reperfusion without selenium injection (*p* value=<0.001, Table 2, Fig. 2) are statistically significant and comparison between group 5, 7 d reperfusion with selenium injection, and group 6, 7 d reperfusion without selenium injection (*p* value=<0.001, Table 2, Fig. 2) are statistically significant and comparison between group 7, 14 d reperfusion with selenium injection, and group 8, 14 d reperfusion without selenium injection (*p* value=0.038, Table 2, Fig. 2) are statistically

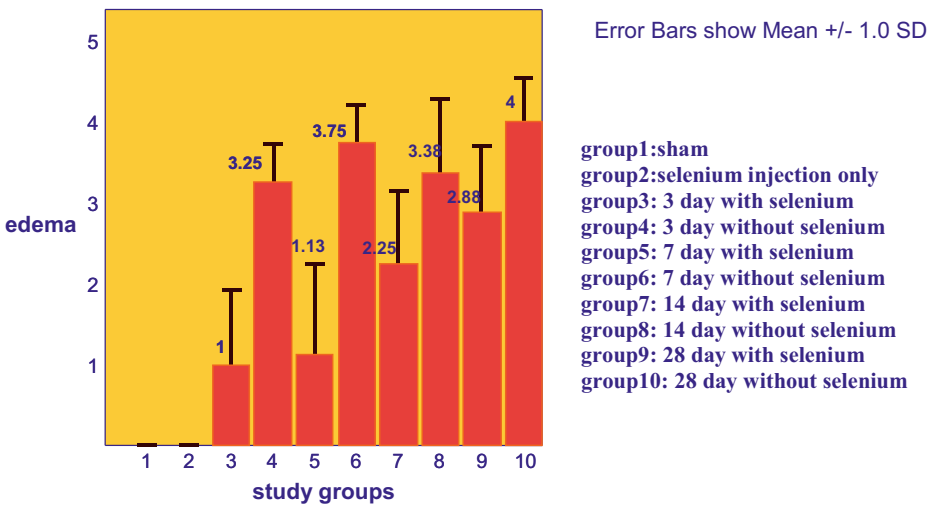

Fig. 2 Edema of the interstitial fluid on the tissue in groups of study

Table 3 Expression of TNF-alpha protein compared at different times of ischemia-reperfusion with and without injection of selenium which each group compared with placebo using Mann-Whitney *U* test

Groups of study	Expression of TNF-alpha protein		*P* value
	Mean of ranks	Mean±SD	
3-d reperfusion without selenium injection (group 4)	9.63	10.6±3.5	0.38
3-d reperfusion with selenium injection (group 3)	7.38	9.12±3.7	
7-d reperfusion without selenium injection (group 6)	12.5	7.25±2.5	<0.001
7-d reperfusion with selenium injection (group 5)	4.5	1.62±.74	
14-d reperfusion without selenium injection (group 8)	12.5	10.5±2.7	<0.001
14-d reperfusion with selenium injection (group 7)	4.5	2.25±2.2	
28-d reperfusion without selenium injection (group 10)	12.5	5.12±1.2	<0.001
28-d reperfusion with selenium injection (group 9)	4.5	0	

significant and comparison between group 9, 28 d reperfusion with selenium injection, and group 10, 28 d reperfusion without selenium injection (p value=0.015, Table 2, Fig. 2) are statistically significant.

Comparison of expression of TNF-alpha protein via immunohistochemistry between groups selenium treated with the placebo corresponding groups suggests that difference between group 5, 7 d reperfusion with selenium injection, and group 6, 7 d reperfusion without selenium injection (p value< 0.001, Table 3, Fig. 3) are statistically significant and comparison between group 7, 14 d reperfusion with selenium injection and group 8, 14 d reperfusion without selenium injection (p value<0.001, Table 3, Fig. 3) are statistically significant and comparison between group 9, 28 d reperfusion with selenium injection and group 10, 28 d reperfusion without selenium injection (p value<0.001, Table 3, Fig. 3) are statistically significant.

Comparison of expression of NF-kappa B protein via immunohistochemistry between groups selenium treated with the placebo corresponding groups suggests that difference between group 3, 3 d reperfusion with selenium injection and group 4, 3 d reperfusion without selenium injection (p value= 0.005, Table 4, Fig. 4) are statistically significant and comparison between group 5, 7 d reperfusion with selenium injection and group 6, 7 d reperfusion without selenium injection (p value=0.021, Table 4, Fig. 4) are statistically significant.

Discussion

Results showed that selenium can reduce edema, mast cell infiltration, and TNF-alpha expression and inactivated NF-kappa B. Simvastatin, amino guanidine, and 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reeducates inhibitors, the most widely used lipid lowering drugs, have been demonstrated to play a neuroprotective role. Various antioxidants have been suggested to reduce ischemia-reperfusion injury. Gholami et al., demonstrated that pre-ischemic administration of simvastatin exhibit neuroprotective properties in I/R nerve injury [13, 14]. Alipour et al. demonstrated that post-ischemic administration of amino guanidine (AG) exhibits protective effect against sciatic nerve I/R injury [15]. Ischemia-reperfusion causes damage to skeletal muscle. This damage may lead to loss of motion skills [2]. Selenium is one of these antioxidants that due to various properties, including anti-apoptotic properties, antioxidant can protect cells against ischemia-reperfusion injury in the heart and liver muscles [12]. This study investigated the effects of selenium in reducing ischemia-reperfusion injury of the gastrocnemius muscle.

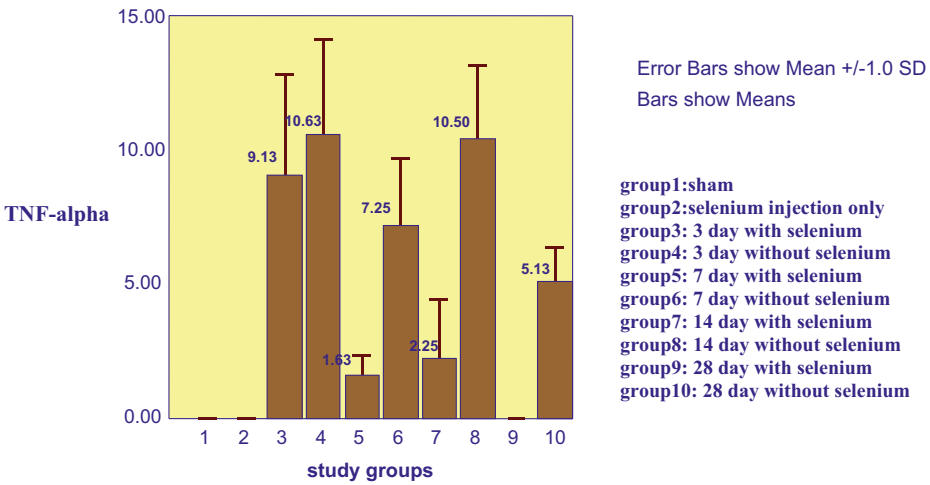

Fig. 3 Expression of TNF-alpha protein in groups of study

Table 4 Expression of NF-kappa B protein compared at different times of ischemia-reperfusion with and without injection of selenium which each group compared with placebo using Mann-Whitney *U* test

Groups of study	Expression of NF-kappa B protein		*P* value
	Mean of ranks	Mean±SD	
3-d reperfusion without selenium injection (group 4)	11.75	8.12±3.5	0.005
3-d reperfusion with selenium injection (group 3)	5.25	3.25±2.4	
7-d reperfusion without selenium injection (group 6)	11.25	10.12±2.2	0.021
7-d reperfusion with selenium injection (group 5)	5.75	6.62±2.4	
14-d reperfusion without selenium injection (group 8)	8.25	1.25±1.4	0.87
14-d reperfusion with selenium injection (group 7)	8.75	1.5±1.7	
28 d reperfusion without selenium injection (group 10)	7.56	5.5±3.2	0.44
28 d reperfusion with selenium injection (group 9)	9.44	6.62±2.3	

To study the effects of selenium on ischemia-reperfusion injury, toluidine blue staining is used to show infiltration of mast cells and hematoxylin-eosin staining is used to show the amount of interstitial edema, inflammatory cell infiltration, and degeneration of muscle fibers and muscle structure disorganization. Mast cells are seen in skeletal muscles, heart muscles, lung, and small intestine in ischemia-reperfusion condition. The results indicate that selenium reduces the amount of mast cells in the gastrocnemius muscle in ischemia-reperfusion. Andrad et al. showed that using an antioxidant called caffeic acid phenethyl ester (CAPE) can reduce the amount of mast cells and neutrophils of ischemia-reperfusion injury in the gastrocnemius muscle [16]. These results are consistent with recent findings. Neutrophils and mast cells are the most important factors of inflammation that enhance the ischemia-reperfusion injury of skeletal muscles [6]. Mast cells play a central role in the ischemia-reperfusion injury. Thus, selenium plays an important role in the prevention of ischemia-reperfusion injury by decreasing mast cells and neutrophils. Histological studies showed that selenium prevents ischemia-reperfusion injury containing edema, tissue structure disorganization, and degeneration. Zendedel et al. showed that selenium with decreased activity levels of NO and increased activity GPX and POX can decrease ischemia-reperfusion injury in hind limb especially sciatic nerve [17].

TNF-α is a factor involved in systemic inflammation and stimulate the acute phase reaction in inflammation [18]. This factor is mainly produced by activated macrophages, although is generated by many other cell types such as CD4 + lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and nerve cells [19]. Finally, TNF-alpha activates NF-κB as an indicator of apoptosis [20]. NF-κB is a transcription factor that is transported to the nucleus and initiate transcription of many factors involved in cell survival and proliferation in response to inflammatory and anti-apoptotic factors [21]. Nuclear factor NF-κB is a protein that activated by proinflammatory cytokines such as IL-1 and TNF-alpha. The role of TNF-alpha is more important to activate NF-κB. NF-κB exists normally in the cytoplasm of cells in an inactive form that is binding with an inhibitor protein called NF-κB inhibitor (IkBs) [21]. In response to a variety of stimuli, such as cytokines TNF-alpha and interleukin-1 (IL1), IkB phosphorylated and subsequently degraded by the proteasome [22]. As a result of this process, NF-κb activated and translocate into nucleus and bind with promoter sites located in areas of immunoregulatory genes and activates them [23]. The results of our study showed that selenium may play important role against ischemia-reperfusion injury by reduction of mast cell infiltration, reduction of TNF-alpha expression and interstitial

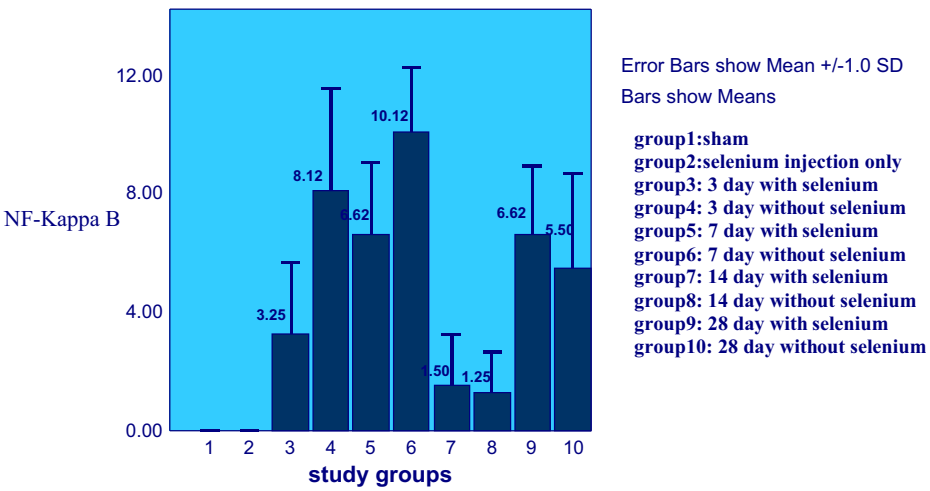

Fig. 4 Expression of NF-kappa B protein in groups of study

edema, and prevention of NF-kappa B activation [23]. Researchers showed that selenium protects ischemic heart from injury with prevention of NF-kappa B activation [24]. These results are consistent with recent findings. Recently, Zendedel et al. showed that selenium with decreased activity levels of NO and increased activity GPX and POX can decrease ischemia-reperfusion injury in hind limb of rat [17]. These results are consistent with recent findings. Taken together, selenium reduces the ischemia-reperfusion injury in the gastrocnemius muscle. There is need for molecular studies to investigate the mechanisms selenium effect on reducing ischemia-reperfusion injury in the gastrocnemius muscle.

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Conflict of interest The authors declare no conflicts of interests.

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