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Selenium Ameliorate Peripheral Nerve Ischemic-Reperfusion Injury via Decreased TNF-α

Abolfazl Zendedel[1,2] · Zahra Gharibi[3] · Khatereh Anbari[4] · Abolfazl Abbaszadeh[5] · Zahra Khanipour khayat[5] · Reza Mohammadrezaei Khorramabadi[6] · Maryam Soleymaninejad[7] · Mohammadreza Gholami[1,3]

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Abstract Selenium is considered as a trace element that plays antioxidant role in the body. So, the aim of this study was to evaluate the effect of selenium on ameliorating of sciatic nerve ischemia-reperfusion injury. Eighty (80) adult male Wistar rats weighing 250–300 g were used. They were divided into 10 groups (n = 8). Then, femoral vessels were obstructed by using 4/0 silk and splitknot techniques. After 3-h ischemia for all the groups, reperfusion was applied for different periods: 3, 7, 14, and 28 days. In half of each experimental group, 0.2 mg/kg selenium was injected intraperitoneally, coinciding with ischemia. After reperfusion, according to the grouping, rats were killed by using high dose of anesthetic drug and then sciatic nerve was removed and fixed. Then, tissue samples were processed and subsequently stained with hematoxylin-eosin, apoptosis, and immunohistochemistry stains. On the third day of reperfusion, the amount of TNF-α as an inflammatory marker of ischemia-reperfusion acute phase increased. On the seventh day of reperfusion, the amount of NF-κB as an apoptotic index and infiltration of mast cells increased in the tissue as a result of development of inflammation. But, on the 14th day of reperfusion, the amount of NF-κB as an apoptotic index decreased to the lowest amount. On the 28th day of reperfusion, the amount of TNF-α as an inflammatory marker decreased to its lowest level. Prescription of selenium concurrent with development of ischemia can reduce the damage caused by sciatic nerve ischemia-reperfusion.

Keywords Selenium · Ischemia · Sciatic nerve · TNF-α

Introduction

Ischemia-reperfusion (IR) is a complex clinical syndrome that affects various organs of the body in specific circumstances, and as its name implies, it includes a stage with decrease or stop in blood perfusion to tissue and after a while, blood reperfusion to that tissue [1]. If cells are reversibly injured due to ischemia, reperfusion can cause improved damaged cells; however, in certain circumstances, reperfusion often paradoxically exacerbates tissue injury by invoking inflammation [1]. As a result, in addition to cells damaged irreversibly due to ischemia, other cells are destroyed in the tissue, this condition is called damage caused by IR, and is an important clinical process that has a significant role in tissue destruction, but it can be controlled with medical interventions [2–6]. Damage induced by IR is caused by free radical production [7–9]. Histopathologic changes subsequent to ischemia are due to blockage in capillary blood flow, and development of necrosis following reperfusion step is recognized as IR injury. Pathophysiology of IR injury includes platelet aggregation,

✉ Mohammadreza Gholami
rezagholami57@gmail.com

1 Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

2 Department of Internal Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

3 Department of Anatomical Sciences, Lorestan University of Medical Sciences, Khorramabad, Iran

4 Department of Social Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

5 Department of Surgery, Lorestan University of Medical Sciences, Khorramabad, Iran

6 Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran

7 Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

oxygen radicals, and interaction between endothelial cells and leukocytes which leads to endothelium damage and capillary obstruction and imperfection in oxygen delivery to nervous tissue [9, 10]. Histopathologic changes of the investigated nerves with IR are associated with nerve fiber degeneration together with nerve edema [9, 10]. Reperfusion nerve damage creates an acute inflammatory response and production of free radicals. Endothelial cells are the main sources of free radicals during the early stages of reperfusion. In the next levels of reperfusion, activated neutrophils and macrophages develop more oxidative stress [10].

Selenium is a trace element and due to its biological function, has oxygen free radical scavenging, antioxidant, and neuroprotective effects [11–13]. Selenium protects DNA, lipid and protein against free radicals [12–14]. Selenium reduces glutathione peroxidase, hydroperoxidase, and lipoperoxidase via a similar activity [12, 13]. Protective effect of selenium against IR injury has been shown in several studies [11–15]. A study on the effects of selenium on brain IR injury has shown therapeutic effect of selenium on prefrontal cortex and hippocampus [12]. Selenium may reduce the levels of TNF-α and IL-1β and therefore in this method, anti-apoptotic effect, together with reduction of inflammatory reaction after IR [12]. Biochemical and histological results support the curative power of this factor [12]. Previously, it was shown that selenium can protect skeletal muscle from IR injury via reduction of edema, mast cell infiltration, TNF-alpha expression, and inactivation of NF-κB, and selenium can ameliorate sciatic nerve recovery via decreased activity levels of NO and increased activity of glutathione peroxidase (GPX) and paraoxonase (POX) in IR lower limb models [13, 16]. Yao et al. showed that dietary selenium (Se) deficiency in chicks which causes accelerated cell apoptosis, increased lipid peroxidation, and reduced GPx activity [17].

Yao et al., in the another research, showed that Selenoprotein W (SelW) played an antioxidant role in mammals, decreased cell apoptosis, and increased cell viability in chicken embryonic myoblasts mediated by endogenous and exogenous H_2O_2 [18].

TNF-α is a factor involved in systemic inflammation and is a member of the cytokine group that stimulates the acute phase of inflammation reaction. This factor is mainly produced by activated macrophages, though is produced by many other types of cells such as of CD4+ cell, NK cell, neutrophil, mast cell, eosinophil, and neuron. TNF-α stimulates macrophages to produce free radicals. TNF-α ultimately lead to activation of NF-κB as an apoptotic index. NF-κB is a transcription factor that is transferred to the nucleus and leads to the transcription of many factors involved in cell survival and proliferation, inflammatory response, and anti-apoptotic factors. NF-κB is a nuclear factor that is made up of protein. Activation of NF-κB is created by pro-inflammatory cytokines such as IL-1 and TNF-α, and the role of TNF-α in the activation of NF-κB is more important. The transcription factor, NF-κB, regulates a wide range of genes involved in cellular responses to inflammation and other types of signals. Normally, NF-κB is available in the cell cytoplasm and is bound to a group of inhibitory proteins called inhibitory protein NF-kB (IkBs). In response to a wide range of stimulants such as cytokines TNF-α and interleukin-1 (IL1), I B is phosphorylated and eventually decomposed by the proteasome. As a result of this process, NF-κB moves into the nucleus and is bound to the location of Kb promoters of many genes which leads to their activation [19].

In general, it can be said that due to the positive effects of selenium in reducing IR injury in various tissues, this antioxidant can be effective in reducing sciatic nerve IR injury. So, the effects of selenium in reducing damage caused by sciatic nerve IR are examined in this study.

Materials and Methods

Eighty (80) Wistar rats (weighing 250–300 g) were studied and divided into 10 groups ($n = 8$). Rats were kept at a temperature of 22 °C in separate cages in an animal house. They were exposed to dark/light cycle with infinite access to standard food ad libitum and water. They were adapted 1 week before the test in the laboratory environment. The studies were conducted in all the groups at the same time.

The rats were grouped as follows:

Group 1. control group (without ischemia-reperfusion)
Group 2. received only 0.2 mg/kg selenium [13] without ischemia-reperfusion (to assess the potential harmful effects).
Group 3. 3 h ischemia and 3 days reperfusion together with injection of 0.2 mg/kg selenium (S + IR3)
Group 4. 3 h ischemia and 3 days reperfusion with injection of placebo (P + IR3)
Group 5. 3 h ischemia and 7 days reperfusion together with injection of 0.2 mg/kg selenium (S + IR7)
Group 6. 3 h ischemia and 7 days reperfusion with injection of placebo (P + IR7)
Group 7. 3 h ischemia and 14 days reperfusion together with injection of 0.2 mg/kg selenium (S + IR14)
Group 8. 3 h ischemia and 14 days reperfusion with injection of placebo (P + IR14)
Group 9. 3 h ischemia and 28 days reperfusion together with injection of 0.2 mg/kg selenium (S + IR28)
Group 10. 3 h ischemia and 28 days reperfusion with injection of placebo (P + IR28)

The rats were anesthetized once intraperitoneally with ketamine HCl (50 mg/kg) and xylazine (5 mg/kg) [10, 20, 21] in accordance with the protocol approved by the Animal Care

and Use Committee and prepared for surgery. To cause ischemia, the inguinal area was 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 4/0 [20, 21] and slipknot technique [20, 21] for 3 hours. After 3 hours, the silk were opened and blood reperfusion to the tissue was re-established in different times as mentioned above. Normal saline and selenium (respectively in experimental and placebo groups), both coinciding with ischemia, were injected intraperitoneally (IP). Behavioral studies were done according to the methods described subsequently. After completion of the behavioral studies, the rats were killed by using additional doses of anesthetic drug and distal part of the sciatic nerve was removed. In order to fix the distal part of the sciatic nerve, it was placed in 10 % formalin for 48 h. Behavioral changes in the animals were examined by someone who was blind to the study and based on gait, toe spread, racing reflex, and pinch sensitivity at the end of the reperfusion phase. Walking (gait) was graded between zero (no actions) and 3 (normal). Grades 1 and 2 represent the severe and slight defect. Toe spread was graded between zero (absent) and 3 (normal). Grades 1 and 2 indicated weak and gentle symmetry, respectively. Pinch sensitivity was graded between zero (no sensitivity) and 2 (normal). Racing reflex was graded between zero (no reflexes) and 3 (normal). Total scores of the four parameters varied from zero to eleven [20, 21].

Situation of Injury Induced by IR To evaluate situation of injury induced by IR in the sciatic nerve, 2 parameters including endoneurial edema and ischemic fiber degeneration were examined (Table 1). To assess endoneurial edema, after passage and sectioning of the fixed samples, hematoxylin and eosin staining was done. At the end of the process, the samples were evaluated based on the severity and spread of edema in five degrees as follows: Zero = normal, 1 = slight edema, 2 = moderate edema, 3 = severe edema and 4 = severe and widespread edema. To evaluate the ischemic fiber degeneration, Gomori's trichrome stain was used. In each nerve fascicle, percentage of the fibers undergoing degeneration was estimated and the mean values were calculated and ranked between 0 and 4 % (more than 2 %), between 3 and 25 %, between 26 and 50 %, between 51 and 75 %, and more than 75 % [20, 21].

Table 1 In this table, presented histopathology data that include edema and ischemic fiber degeneration

Group	Ischemic fiber degeneration(IFD)		Edema	
	P value	Mean ± SD	*P* value	Mean ± SD
S + IR3	0.038	2 ± 0.75	1	2 ± 0.75
P + IR3		3 ± 0.75		2 ± 0
S + IR7	0.001	2 ± 0.75	0.038	2 ± 0.75
P + IR7		4 ± 0.92		3 ± 0.75
S + IR14	0.001	1 ± 0.75	0.088	2 ± 1.06
P + IR14		4 ± 0.75		3 ± 0.92
S + IR28	0.01	1 ± 0.75	0.065	2 ± 0.75
P + IR28		4 ± 2		3 ± 0.92

Selenium in the early stage (the first week of reperfusion) and late stage (until 28 days reperfusion) can decrease IFD, significantly but cannot decrease edema until 14 days reperfusion injury significantly. In the 14 days, reperfusion selenium-treated groups show decrease in the neural edema in the comparison with placebo. Each group compared with that of the corresponding control, Mann-Whitney U test. All data expressed Mean ± SD and results considered significant at $p \leq 0.05$ result

Immunohistochemically Studies

TNF-alpha and NF-κB expression was performed according to the method of AbD Serotec and cell signal procedure, respectively, with slight modifications which were previously described by Gholami et al. [13]. The results were analyzed by specialists that are blinded to the study.

Results

Behavioral Scores

Mean value of the behavioral changes in group that received selenium and the control group, by using the Mann-Whitney test, showed difference between S + IR3 and P + IR3 which was statistically significant (*P* value < 0.001) (Table 2), difference between S + IR7 and P + IR7 which was statistically significant (*P* value < 0.001) (Table 2), difference between S + IR14 and P + IR14 which was statistically significant (*P* value = 0.006) (Table 2), and difference between S + IR28 and P + IR28 which was not statistically significant (*P* value = 1) (Table 2).

Edema

Evaluating the severity of tissue edema in the group that received selenium and control group by using the Mann-Whitney test showed that the difference between S + IR3 and P + IR3 groups was not statistically significant (*P* value = 1) (Table 1), difference between S + IR7 and P + IR7 groups was statistically significant (*P* value = 0.038) (Table 1), difference between S + IR14 and P + IR14 groups was not statistically significant (*P* value = 0.088) (Table 1), and difference between S + IR28 and P + IR28 groups was not statistically significant (*P* value = 0.065) (Table 1 and Figs. 1 and 2).

Table 2 This table presented behavioral scores, TNF-alpha (an inflammatory protein), and NF-κB (controls transcription of DNA)

Groups	Behavioral scores		NF-κB		TNF-alpha	
	P value	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD
S + IR3	<0.001	10 ± 1.06	<0.001	2 ± 0.75	0.015	8 ± 0.92
P + IR3		5.5 ± 0.53		7 ± 1.51		10.13 ± 1.72
S + IR7	<0.001	11 ± 0	<0.001	5 ± 0.75	<0.001	1 ± 0.75
P + IR7		8.5 ± 0.53		8 ± 0.75		6 ± 0.75
S + IR14	0.006	6 ± 1.06	1	1 ± 0.75	0.001	1 ± 0.75
P + IR14		4 ± 1.06		1 ± 0.75		9 ± 1.06
S + IR28	1	11 ± 0	1	4 ± 0.75	0.001	0.25 ± 0.46
P + IR28		11 ± 0		5 ± 0.75		4 ± 0.75

Result showed that selenium in the early stage (the first week of reperfusion) and late stage (until 28 days reperfusion) can decrease TNF-alpha expression, inactivated NF-κB, and behavioral scores significantly except 28-day reperfusion. Each group compared with that of the corresponding control, Mann-Whitney *U* test. All data expressed Mean ± SD and results considered significant at $p \leq 0.05$

Ischemic Fiber Degeneration (IFD)

Evaluating the level of ischemic fiber degeneration in the group that received selenium and control group by using the Mann-Whitney test showed that the difference between S + IR3 and P + IR3 groups was statistically significant (*P* value = 0.038) (Table 1), difference between S + IR7 and P + IR7 groups was statistically significant (*P* value = 0.001) (Table 1), difference between S + IR14 and P + IR14 groups was statistically significant (*P* value = 0.001) (Table 1), and difference between S + IR28 and P + IR28 groups was statistically significant (*P* value = 0.01) (Table 1 and Fig. 3).

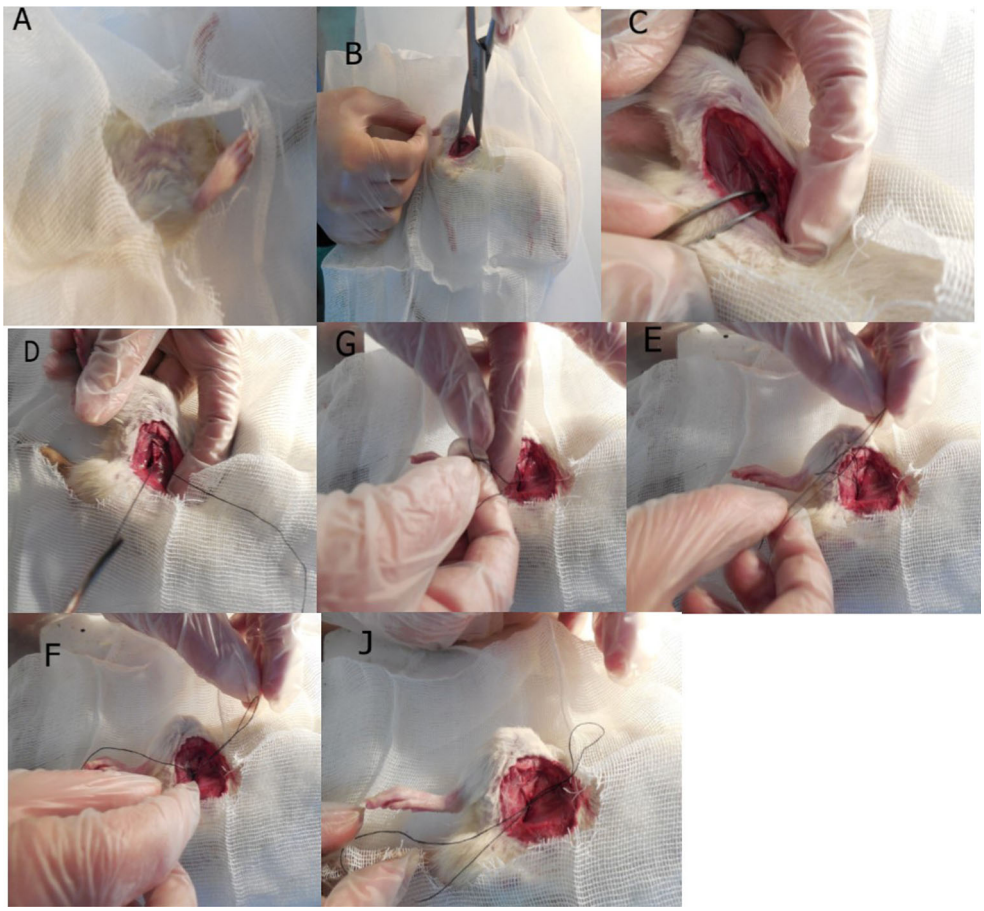

Fig. 1 To create ischemia, the inguinal area has been shaved (*A*), and after disinfection, the femoral artery and vein were carefully separated from the femoral nerve with an inguinal incision (*B*, *C*). Then, the artery and vein were knit using a silk suture 4/0 and slipknot technique for 3 hours (*D*, *G*, *E*, *F*, *J*)

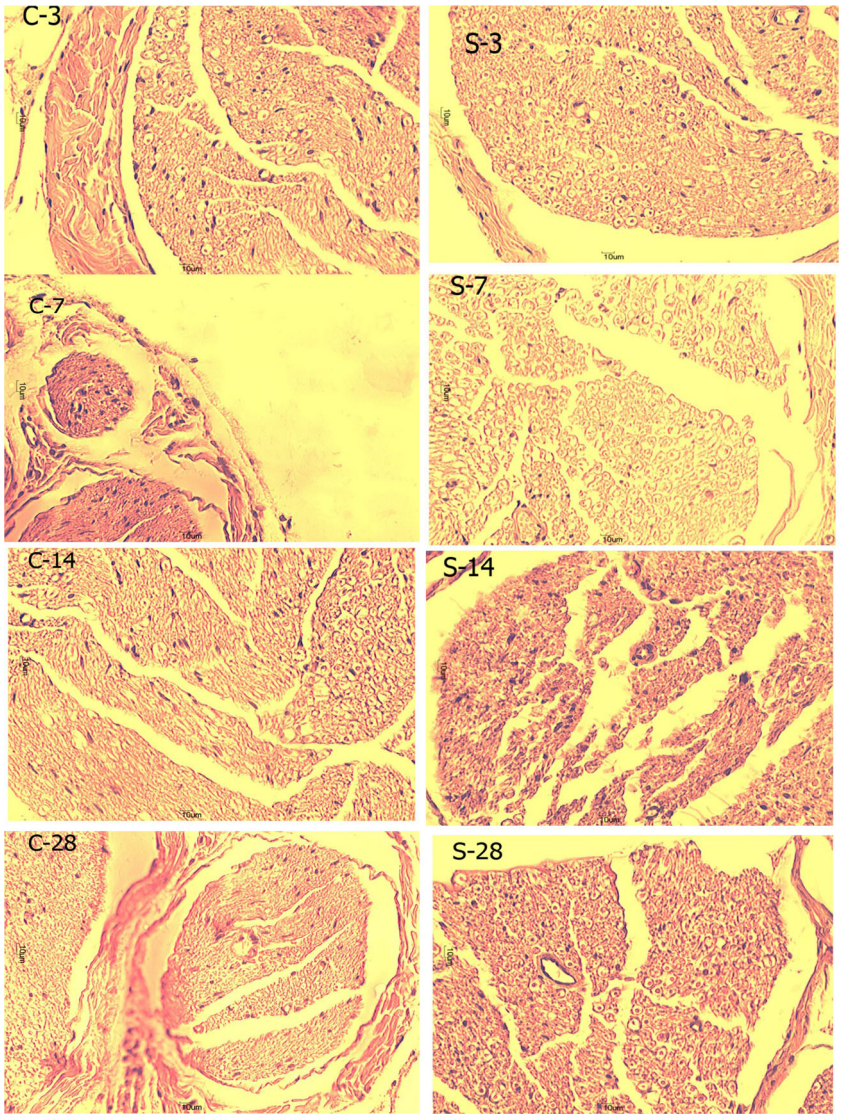

Fig. 2 Endoneurial edema showed in the groups of study. *C* control, *S* selenium. H and E stain. *C-3* (P + IR3), *S-3* (S + IR3), *C-7* (P + IR7), *S-7* (S + IR7), *C-14* (P + IR14), *S-14* (S + IR14), *C-28* (P + IR28), and *S-28* (S + IR28)

Immunohistochemistry (TNF-Alpha and NF-κB)

TNF-alpha expression between some selenium-treated groups such as S + IR3 and P + IR3 groups (P value = 0.015), S + IR7 and P + IR7 (P value < 0.001), S + IR14 and P + IR14 (P value = 0.001), and S + IR28 and P + IR28 (P value = 0.001), with the corresponding control, is statistically significant (Fig. 4). NF-κB expression results showed that comparison between S + IR3 and P + IR3 groups (P value < 0.001) and S + IR14 and P + IR14 (P value = 0.001) are statistically significant (Fig. 5).

Discussion

As mentioned earlier, selenium has strong antioxidant properties which has been proven in many studies on human and laboratory animal models in different situations of IR, such as myocardial infarction, open heart surgery, organ transplantation, bladder IR, brain trauma, and brain IR; so, this study aimed to examine possible beneficial effect of reducing sciatic nerve IR injury in adult male rats. Fortunately, this study findings support the beneficial effects of preventing tissue edema, fiber degeneration, and recovery of behavioral functions.

The results of the present study indicate that the drug's effects on behavioral capabilities could be evaluated in two phases. Phase 1 is short-term reperfusion phase. In this phase, results of the third and the seventh days were evaluated. Comparison between the results of behavioral score mean values showed that in the S + IR3 and P + IR3 groups, selenium in this phase had significant effect on behavioral and motor capabilities in rats (P value = 0.001). Comparison between the results of behavioral score mean values showed that in the S + IR7 and P + IR7 groups, selenium in this phase had significant effect on the recovery of behavioral and motor capabilities in rats (P value = 0.001). Phase 2 is long-term reperfusion phase. In this phase, results of the 14th and the 28th days of reperfusion were evaluated. During this phase, the

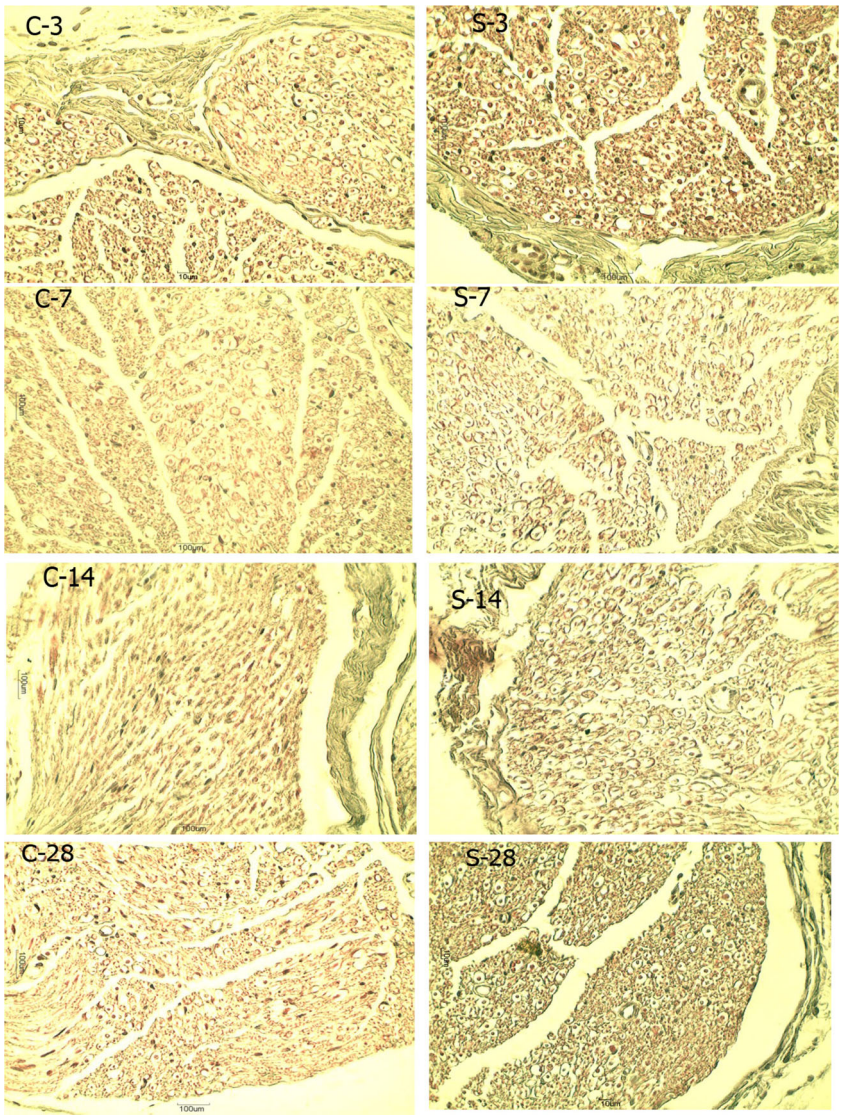

Fig. 3 Ischemic fiber degeneration showed in the groups of study. *C* control, *S* selenium. Gomori's trichrome stain. *C-3* (P + IR3), *S-3* (S + IR3), *C-7* (P + IR7), *S-7* (S + IR7), *C-14* (P + IR14), *S-14* (S + IR14), *C-28* (P + 28), and *S-28* (S + IR28)

behavioral and motor capabilities showed improvement. Comparison between results of behavioral score mean values showed that in S + IR14 and P + IR14 groups, selenium in this phase had significant effect on the behavioral and motor capabilities in rats (*P* value = 0.006). Comparison between results of the behavioral score mean values showed that S + IR28 and P + IR28 groups, selenium during this phase had significant effect on the recovery behavioral and motor capabilities in rats (*P* value = 0.065). The results are consistent with that of Mitsui et al. [22].

The results showed that selenium in the early (the first week of reperfusion) and late stages (until 28 days reperfusion) can reduce IFD significantly, but cannot reduce edema significantly until the 14th day of reperfusion. In the 14th day of reperfusion, selenium-treated groups showed decrease in the neural edema in comparison with the control group.

Recently, it was shown that selenium with reduced mast cells infiltration, TNF-alpha expression, interstitial edema, and prevention of activation of NF-kappa B can play an important role in the reduction of ischemia-reperfusion injury of the gastrocnemius muscle [13]. Recently, Zendedel et al. [16] showed that selenium with decreased activity levels of NO and increased activity of GPX and POX can ameliorate ischemia-reperfusion injury in hind limb of rat. These results are consistent with recent findings.

Wang et al. [23] proved that TNF-alpha plays an essential role in the pathogenesis of peripheral nerve ischemia-reperfusion injury, possibly, partly through the activation of NF-κB. Researchers showed that selenium protects against heart ischemic reperfusion injury by NF-κB inactivation [24]. These results are quite consistent with the results of the present research. In the present survey, first, TNF-α as an inflammatory factor increased on the third day and it seems like TNF-α by inactivating IKB, led to release of NF-kB and its migration into nucleus in the next time period as selenium injection on the seventh day of reperfusion led to a reduction of TNF-α which also led to increased levels of NF-kB in the

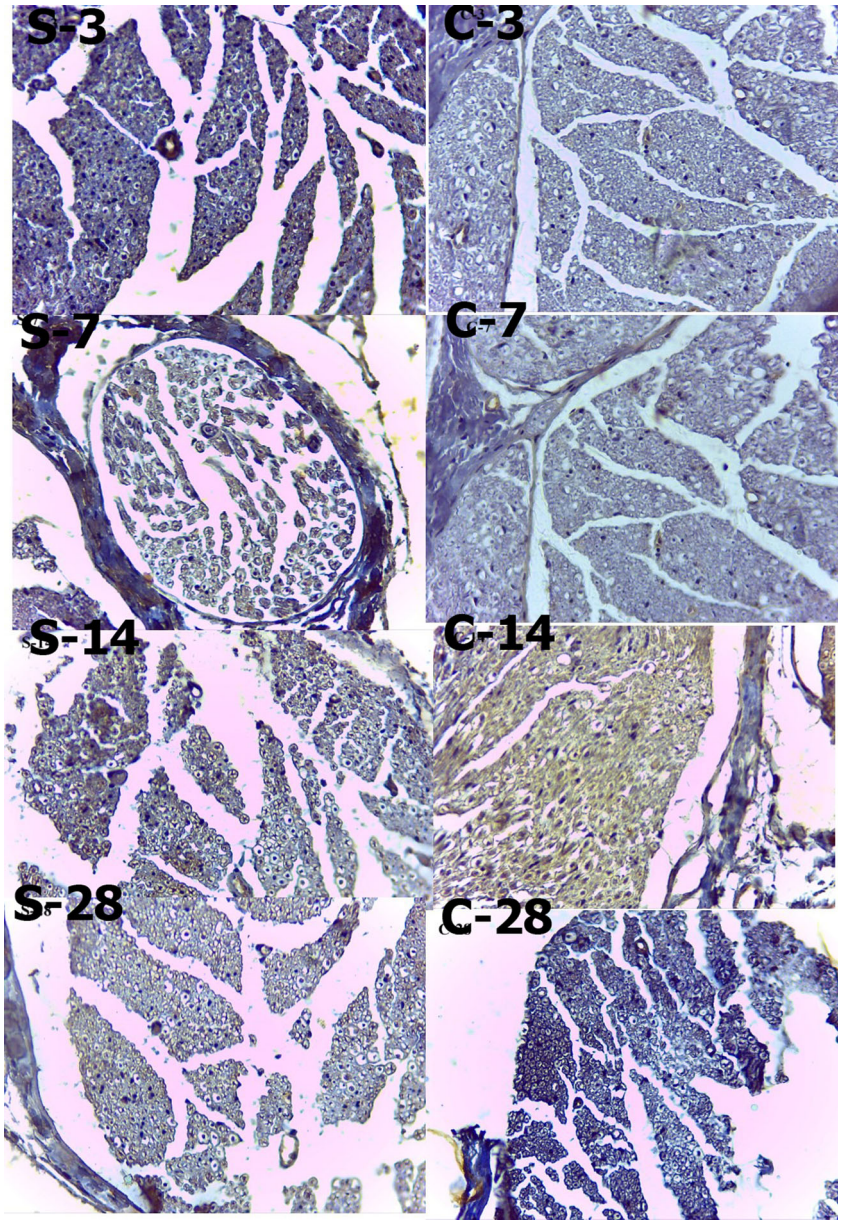

Fig. 4 Microscopic TNF-alpha expression findings in different groups of study. *C-3* (P + IR3), *S-3* (S + IR3), *C-7* (P + IR7), *S-7* (S + IR7), *C-14* (P + IR14), *S-14* (S + IR14), *C-28* (P + 28), and *S-28* (S + IR28)

cytoplasm, and on the seventh day of reperfusion, highest amount of protein NF-κB was detected in the cytoplasm.

Selenium led to reduction in the number of star cells, liver fibrosis, and increased expression of matrix metalloproteinase-9 (MMP-9) in a model of liver fibrosis. Selenium also led to decrease in expression of MMP-13, increase in expression of tissue inhibitor of MMP-1 and MMP-2, and prevention of the reduction of type 2 collagen by T2 toxin in human chondrocytes [25]. Lee et al. [26] showed that selenium inhibits cell death by inhibition of TNF-α in neuroblastoma cells.

In another study in the hyperlipidemia control group, increased cardiac enzymes and TNF-α in cardiac cells were observed, while pretreatment with injection of selenium subcutaneously reduced the TNF-α levels which is an indication of protective effects of selenium on cardiovascular function [14].

These findings are consistent with the results of the current investigation based on protective effect of selenium by reducing the expression of inflammatory proteins TNF-α and prevention from decrease in cytoplasmic NF-κß against nerve tissue damage caused by ischemia-reperfusion.

Selenium is a trace element and is a component of glutathione peroxidase. It protects the heart from reperfusion damage caused by ischemia, but the mechanism of this protection is not fully understood [27]. These data suggest that selenium protects the heart against damage caused by ischemia-reperfusion due to activity in restoration surface and inactivating NF-κB in heart ischemia-reperfusion [27].

A study on the effect of selenium on brain ischemia-reperfusion injury showed the therapeutic effect of selenium on prefrontal cortex and hippocampus [25]. Selenium may

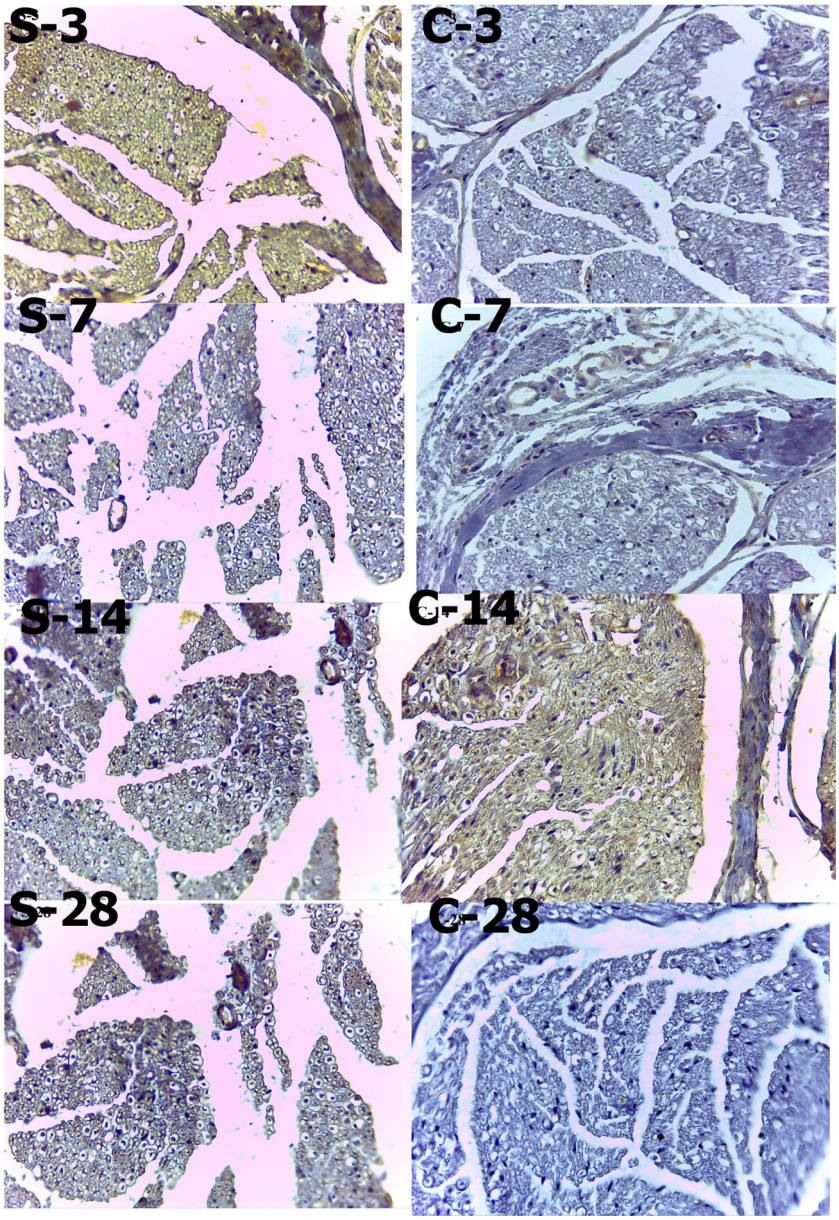

Fig. 5 Microscopic NF-κB expression findings in different groups of study. *C-3* (P + IR3), *S-3* (S + IR3), *C-7* (P + IR7), *S-7* (S + IR7), *C-14* (P + IR14), *S-14* (S + IR14), *C-28* (P + 28), and *S-28* (S + IR28)

reduce the levels of TNF-α and IL-1β and therefore in this method, anti-apoptotic effect together with reduction in inflammatory reaction after ischemia-reperfusion [27]. Biochemical and histological results support the curative power of this factor [27].

The consumption of selenium supplements has shown that selenium reduces the incidence of Keshan disease in populations in endemic areas with selenium deficiency and cardiomyopathy [12]. These results are consistent with the results of the current study; both suggest beneficial effect of selenium in reducing ischemic reperfusion injury. These results and observations are in line with the results of the present study that suggest a beneficial effect of selenium on reduction of ischemic reperfusion injury in various tissues.

The researchers, during a study in 2012, examined the effects of selenium on the ovaries of ischemia-reperfusion-injured rats. Single dose of selenium was administered as 0.2 mg/kg intraperitoneally, 30 min before reperfusion (IP). Then, the level of malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase activity (SOD), catalase activity (CAT), and glutathione peroxidase activity (GPX) were measured in ovarian tissue. The results showed that selenium is effective in the prevention of tissue damage caused by ischemia-reperfusion in rat ovaries [28].

Multiple pre-clinical studies suggest that the development of oxidative stress caused by myocardial injury through ischemia and ischemia-reperfusion is reduced predominantly by selenoproteins and glutathione peroxidase [12]. Selenium deficiency led to deterioration, and selenium supplementation

led to elimination of myocardial injury [12]. The results of myocardial histologic analysis also showed reduced tissue damage in the groups that received these drugs. Ultimately, the authors concluded that antioxidant drugs that were studied in this research can help to reduce the damage caused by myocardial ischemia-reperfusion. The results of the current study and that of other studies are consistent and are another reason for antioxidant and protective properties of selenium against tissue damage caused by ischemia-reperfusion.

Heyland et al. [29] concluded that the use of selenium, due to its antioxidant properties, decreased mortality in chronic patients exposed to free radical damage, while other antioxidants and vitamins have no such effect. These findings are consistent with the results of the current study and indicate the beneficial antioxidant and protective effects of selenium against tissue damage caused by ischemia-reperfusion.

In another study, Turker et al. [30, 31] showed that selenium has a protective effects by inhibiting the formation of free radicals and supporting oxidation system and antioxidant and redox signaling. Yao et al. showed that dietary selenium (Se) and Selenoprotein W decreased cell apoptosis in chickens [17, 18]. These results are consistent with the above results and are another reason for antioxidant and protective properties of selenium against tissue damage caused by ischemia-reperfusion.

Conclusion

In general, according to the results of the current study, it can be concluded that the injection of selenium can reduce sciatic nerve ischemia-reperfusion injury. This property can be used in conditions, such as organ transplantation, rhabdomyolysis, and other nerve injuries, to reduce damage.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

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