Original Article

MESNA (2-Mercaptoethanesulfonate) Attenuates Brain, Heart, and Lung Injury Induced by Carotid Ischemia-Reperfusion in Rats

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Abstract

Background: Ischemia-reperfusion (I/R) causes organ dysfunction as a result of the increased formation of various reactive oxygen metabolites, infiltration of inflammatory cells, interstitial edema, cellular dysfunction, and tissue death. **Aim:** The study aimed to investigate the cytoprotective effect of 2-mercaptoethanesulfonate (MESNA) against tissue damage in rats exposed to carotid ischemia-reperfusion. **Materials and Methods:** Twenty-four male Wistar albino rats were divided into four groups (n = 6): sham, carotid I/R, I/R + MESNA (75 mg/kg), and I/R + MESNA (150 mg/kg) groups. To induce ischemia in rats, the carotid arteries were ligated with silk sutures for 10 min; the silk suture was then opened, and 1 h reperfusion was done. MESNA (75 and 150 mg/kg) was administered intraperitoneally 30 min before ischemia-reperfusion. Tissue samples from the animals were taken for histological examination, while the serum levels of some biochemical parameters were utilized to evaluate the systemic alterations. ANOVA and Tukey's *post hoc* tests were applied with a significance level of 5%. **Results:** The ischemia-reperfusion-induced tissue damage as evidenced by increase in serum levels of alanine transaminase, aspartate aminotransferase, alkaline phosphatase, malondialdehyde, lactate dehydrogenase, and matrix metalloproteinases (MMP-1, -2, -8) was significantly ($P < 0.05$–0.0001) reversed after treatment with MESNA in a dose-dependent manner. Treatment with MESNA (75 and 150 mg/kg), significantly ($P < 0.05$–0.0001) decreased the I/R-induced increase in serum tumor necrosis factor-alpha (TNF-α) and Interleukin-1-beta (IL-1 β). **Conclusion:** The results of this study suggest that MESNA has a protective effect on tissues by suppressing cellular responses to oxidants and inflammatory mediators associated with carotid ischemia-reperfusion.

Keywords: *Carotid artery, Ischemia, MESNA, Oxidative stress, Reperfusion*

Introduction

Carotid ischemia is a serious health concern because of its high morbidity and mortality rates.[1] Ischemia-induced tissue damages are well defined, leading first to damage of brain tissue and then to pathological damage of distant organs such as the lungs and the heart. While reperfusion is essential to reverse the effects of ischemia, it also causes additional damage to tissues in severe cases. Oxidative stress, infiltration of inflammatory cells, and disruption of the blood-brain barrier are some of the distinct mechanistic pathways of reperfusion injury that can result in cerebral edema and severe neurological dysfunctions.[2]

Reduced blood flow to the brain if left untreated can lead to conditions such as stroke, cardiac arrest, pulmonary embolism, and even death.[1] Reperfusion

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increases the levels and activation of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and Interleukin-1-beta (IL-1 β), and proteolytic enzymes such as matrix metalloproteinase (MMP), leading to inflammation and degeneration of tissues.[3] It is well known that the acute inflammatory response leads to tissue damage through the production and release of free radicals and cytotoxic proteins into the extracellular fluid.[4] Therefore, the need for an anti-inflammatory agent with immunomodulatory and free radical-scavenging properties is increasing rapidly, since inflammatory mediators play an increasingly vital role in ischemia-reperfusion injury.[5]

2-mercaptoethanesulfonate (MESNA) is a synthetic sulfur-containing antioxidant and anti-inflammatory drug used to prevent nephrotoxic side effects associated with chemotherapy drugs.[6] Studies have shown that MESNA prevents ischemia-reperfusion-induced renal, intestinal, and hepatic oxidative injury in rats,[4,7,8] burn-induced renal injury in rats,[9] ulcerative colitis,[10] and several other inflammatory conditions.[11] MESNA exerts these effects by regulating the activation of proteolytic enzymes along with the expression of cytokines and suppression of free radicals.[4,12] Due to these cytoprotective effects, MESNA may effectively limit the deleterious effects of proinflammatory mediators and free radicals.

Several experimental studies have shown therapeutics using different agents to prevent ischemia-reperfusion injuries.[13-17] However, several clinical trials of therapy to treat ischemia-reperfusion injury have not yielded sufficient significant results,[18,19] and there are also no studies on the effect of MESNA on carotid ischemia-reperfusion. Therefore, based on an extensive literature search, we administered different doses of MESNA to investigate whether MESNA confers protection against experimentally induced carotid ischemia-reperfusion in rats by examining the histological changes in brain, heart, and lung tissues and some serum biochemical parameters.

Materials and Methods

All experimental procedures used were approved by the Near East University Ethics Committee with protocol number 2021/139-139. A total of 24 male Wistar albino rats, about 3 months old and weighing 250–300 g, were used for this study. All animals were anesthetized (100 mg/kg ketamine and 10 mg/kg xylazine; i.p.) during all surgical procedures.

Experimental design

The rats were divided into four groups (n = 6) [Figure 1]. In the sham-operated control group, the common carotid artery was excised without occlusion. The carotid I/R group was exposed to ischemia-reperfusion and treated with normal saline (intraperitoneally). The two MESNA-treated groups received MESNA (Uromitexan 75 mg/kg and 150 mg/kg, i.p.; Baxter, Germany), respectively, 30 minutes before ischemia-reperfusion. The MESNA dose used in this study was modified based on previous studies.[8,11,20]

Carotid artery ischemia-reperfusion procedure

The intraluminal thread method as described by Handayani *et al.*[21] was used to induce ischemia-reperfusion of the common carotid artery. The rats were placed supine, then the abdomen shaved and cleaned with antiseptic solution (povidone iodine 10%). Abdominal incision was made 3 cm from the midline of the trachea, followed by exposure of the aorta and other visceral arteries. The common carotid arteries were exposed by midline blunt dissection of the sternohyoid muscle. The common carotid artery was then ligated bilaterally with 4/0 silk sutures at the level of the 4°–5° tracheal ring. The common carotid arteries were occluded for 10 min to induce ischemia and then subjected to 1 h of reperfusion. One hour after reperfusion, all animals were decapitated, and blood and tissue samples of the brain, heart, and lungs were collected.

Biochemical assays

Sera samples were centrifuged for 10 min at 1500 rpm and stored at -80°C. To assess the severity of cellular injury, serum levels of alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) were measured using an automated analyzer (BS240-Vet, Mindray, Shenzhen, China). TNF-α, IL-1β, MMP(-1, -2, -8), and TIMP-1 serum levels were measured using rat-specific ELISA test kits (ELR-TNF-α and ELR-IL1β, RaybioTech Inc., GA, US). Assays were washed as described by the manufacturer, using an automated microtiter washer (MW-12A Microplate Washer, Mindray, Shenzhen, China), and absorbances at 450 nm were measured using a microtiter plate reader (MR-96A Microplate Reader, Mindray, Shenzhen, China).

Malondialdehyde (MDA), a stable lipid peroxidation product, was measured in serum as previously described by Beuge and Aust.[22] The assay was based on reaction with thiobarbituric acid (TBA) at 100°C in an acidic environment, and the absorbance of the reaction mixture was measured at 530–540 nm using a microplate reader (VersaMax Tunable Microplate Reader, Molecular Devices LLC, CA, USA).

Histopathological assessment

After the decapitation of the animals, the tissue samples of brain, heart, and lungs were washed thoroughly with

saline. The samples were placed in 10% formaldehyde and routinely processed by embedding in paraffin. Tissue sections (5–6 mm) were stained with hematoxylin and eosin and examined under a light microscope. An experienced histopathologist who was blinded to the study design performed the histologic assessments.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA). All data were expressed as mean ± (SEM). Datasets were compared using one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. Values of $P < 0.05$ were considered statistically significant.

Results

Biochemical results

Effects of MESNA on serum enzyme activities

Analysis of serum levels ALP, AST, ALT, and LDH levels in the carotid I/R group showed a highly significant increase compared with the sham, I/R + MESNA (75 mg/kg), and I/R + MESNA (150 mg/kg) groups ($P < 0.05$–0.001). The carotid I/R-induced increase in serum enzyme levels significantly decreased after treatment with MESNA (75 and 150 mg/kg) ($P < 0.05$–0.01). However, there was no significant difference between the sham and either MESNA treatment groups, nor between the I/R + MESNA (75 and 150 mg/kg) groups ($P > 0.05$) [Table 1].

Effects of MESNA on serum malondialdehyde levels

The carotid I/R group showed a significant increase in serum MDA levels compared with the other groups ($P < 0.001$). MESNA (75 and 150 mg/kg) significantly reversed the carotid I/R-induced increase in serum MDA levels ($P < 0.001$). The I/R + MESNA (75 and 150 mg/kg) groups showed no significant differences in MDA levels compared with the sham group ($P > 0.05$). Serum MDA levels were not significantly different between both MESNA (75 and 150 mg/kg) groups ($P > 0.05$) [Table 2].

Effects of MESNA on serum matrix metalloproteinases (MMP-1, -2, -8) and tissue inhibitor of metalloprotease-1 (TIMP-1) expression

In the carotid I/R group, the serum levels of MMP (-1, -2, -8**)** and TIMP-1 levels increased significantly compared to the other groups ($p < 0.05$–0.0001). After treatment with MESNA (75 mg/kg and 150 mg/kg), serum levels of

Table 1: Serum levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH)

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
ALP (U/L)	60.67±7.86	109±10.03***	77.75±2.01$^{\#}$	68.37±6$^{\#\#}$
AST (U/L)	129±4.40	161.1±5.97**	129.8±6.69$^{\#\#}$	132.4±5.48$^{\#\#}$
ALT (U/L)	27.18±1.45	114.4±26.03**	35.35±7.40$^{\#\#}$	36.62±7.51$^{\#\#}$
LDH (U/L)	1360±153.7	2833±400.2**	1593±141.2$^{\#\#}$	1848±160.2$^{\#}$

Values are expressed as mean±standard error (n=6); **P<0.01, ***P<0.001 vs. sham; # P<0.05, ##P<0.01, vs. carotid I/R

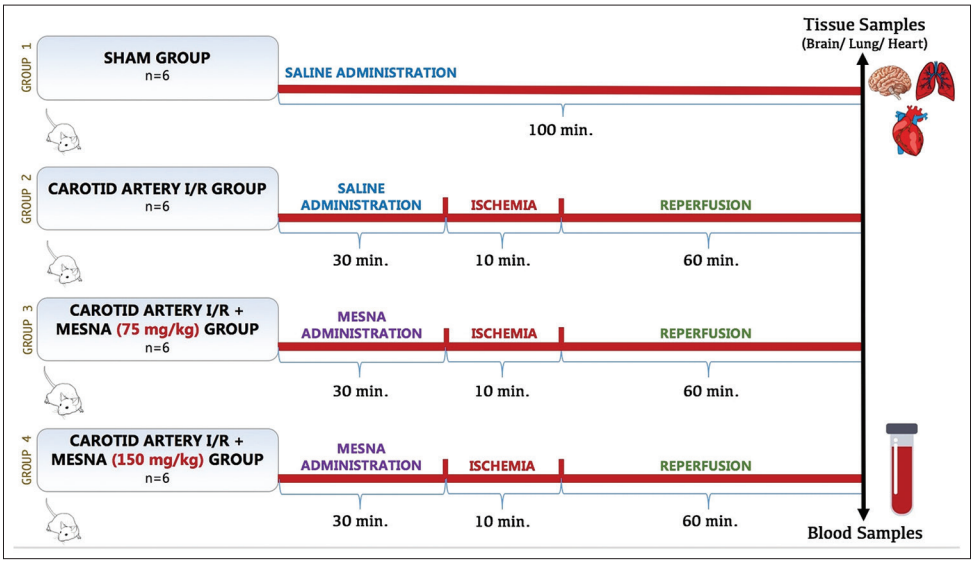

Figure 1: Schematic diagram of the experimental design

Table 2: Serum malondialdehyde (MDA) levels

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
MDA (µmol/L)	6.62±0.90	50.35±11.42***	9.67±1.13###	7.42±1.12###

Values are expressed as mean±standard error (n=6); ***P<0.001 vs. sham; ###P<0.001 vs. carotid I/R

Table 3: Serum matrix metalloproteinases (MMP-1, -2, -8) and tissue inhibitor of metalloprotease-1 (TIMP-1) levels

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
MMP-1 (pg/mL)	1.51±0.15	3.82±0.19****	2.49±0.28##	2.30±0.20###
MMP-2 (pg/mL)	30.93±5.90	56.32±6.0**	28.69±2.27##	22.61±1.57###
MMP-8 (pg/mL)	72.39±7.71	190.7±43.07**	96.48±4.75#	82.79±4.74#
TIMP-1 (pg/mL)	383.7±45.13	899.2±71.42****	640.2±69.94#*	405.6±62.83###

Values are expressed as mean±standard error (n=6); *P<0.05, **P<0.01, ****P<0.0001 vs. sham; #P<0.05, ##P<0.01, ###P<0.001 vs. carotid I/R

Table 4: Serum tumor necrosis factor-alpha (TNF-α) and Interleukin-1-beta (IL-1β) levels

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
TNF-α (pg/mL)	13.36±3.10	34.17±6.17**	19.69±1.58#	8.59±1.61###
IL-1β (pg/mL)	154.1±17.35	332.2±25.15****	146.3±16.89####	113.4±15.79####

Values are expressed as mean±standard error (n=6); **P<0.01, ****P<0.0001 vs. sham; #P<0.05, ###P<0.001, ####P<0.0001 vs. carotid I/R

Table 5: Effects of ischemia-reperfusion and its treatment with MESNA on brain tissue

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
Brain neutrophil layout	0.28±0.05	2.35±0.19****	1.43±0.05****####	1.23±0.04****####
Brain capillar intensity	0.25±0.02	2.4±0.07****	1.7±0.05****####	1.23±0.04****####
Neuronal degeneration	0.33±0.05	2.9±0.07****	2.55±0.04****##	2.26±0.06****####

Values are expressed as mean±standard error (n=6); ****P<0.0001 vs. sham; ##P<0.01, ####P<0.0001 vs. carotid I/R

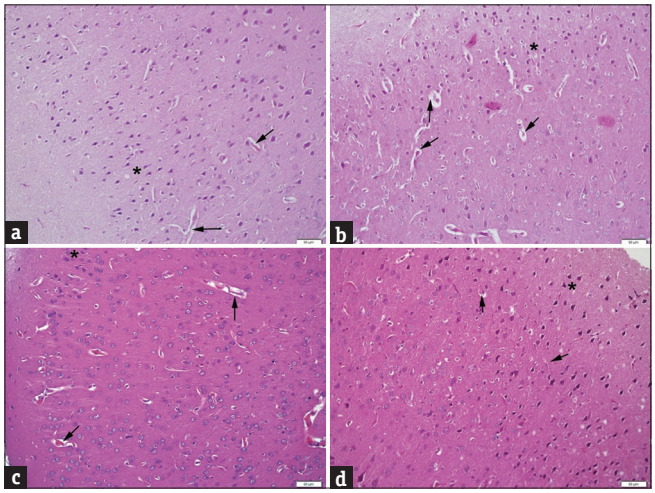

Figure 2: Microscopic examination of brain tissues. (a) Sham group: regular neuropil morphology (*) and capillaries (arrows); (b) carotid I/R group: degenerated neurons (*) and capillaries (arrows); (c) I/R + MESNA 75 mg/kg group: reduced neuronal degeneration (*) capillaries (arrows); (d) I/R + MESNA 150 mg/kg group: regenerated neuronal neurons (*) capillaries (arrows). (H.E, Bar 50 µm)

MMP (-1, -2,-8) and TIMP-1 decreased significantly compared to the carotid I/R group (p < 0.05–0.001); however, there was significant increase in serum TIMP-1 level after treatment with MESNA (75 mg/kg) compared with the sham group (P < 0.05). There was no significant difference between the I/R + MESNA (75 and 150 mg/kg) groups in terms of MMP (-1, -2,-8), and TIMP-1 levels (P > 0.05) [Table 3].

Effects of MESNA on serum tumor necrosis factor-alpha (TNF-α) and Interleukin-1-beta (IL-1β) expression

Analysis of serum TNF-α and IL-1β levels showed a significant increase in the carotid I/R group compared with the other groups (P < 0.05–0.0001). The I/R + MESNA (75 and 150 mg/kg) groups showed no significant differences compared with the sham group (P > 0.05). MESNA (75 and 150 mg/kg) significantly reversed the carotid I/R-induced increase in serum TNF-α and IL-1β levels (P < 0.05–0.0001). There was no significant difference between the I/R + MESNA (75 and 150 mg/kg) groups in terms of TNF-α and IL-1β levels (P > 0.05) [Table 4].

Histopathological results

Brain morphometric result

Brain neutrophil layout, brain capillary intensity, and neuronal degeneration scores were significantly higher in the carotid I/R group than in the sham group (P < 0.0001). After treatment with MESNA (75 mg/kg and 150 mg/kg), the values of brain histological features decreased significantly compared to the sham and carotid I/R groups (P < 0.0001). However,

Table 6: Effects of ischemia-reperfusion and its treatment with MESNA on lung tissue

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
Lung congestion	0.61±0.06	2.95±0.08****	2.11±0.15****####	1.78±0.08****####
Alveolar degeneration	0.51±0.06	2.86±0.18****	2.21±0.14****####	1.68±0.08****####++
Interstitial oedema	0.65±0.07	2.96±0.06****	2.13±0.66****####	1.61±0.13****####++

Values are expressed as mean±standard error (n=6); ****P<0.0001 vs. sham; ####P<0.0001 vs. carotid I/R; ++P<0.01: MESNA 75 vs. MESNA 150 mg/kg

Table 7: Effects of ischemia-reperfusion and its treatment with MESNA on heart tissue

	Sham	Carotid I/R	I/R + MESNA 75 mg/kg	I/R + MESNA 150 mg/kg
Heart congestion	0.5±0.08	2.8±0.03****	2.3±0.07*	1.8±0.16#
Cardiomyocyte degeneration	0.3±0.03	2.51±0.04****	2.08±0.06****###	1.78±0.06****####++
Inflammation	0.28±0.04	2.3±0.05****	1.733±0.06*	1.4±0.07#

Values are expressed as mean±standard error (n=6); *P<0.05, ****P<0.0001 vs. sham; #P<0.05, ###P<0.001, ####P<0.0001 vs. carotid I/R; ++P<0.01: MESNA 75 vs. MESNA 150 mg/kg

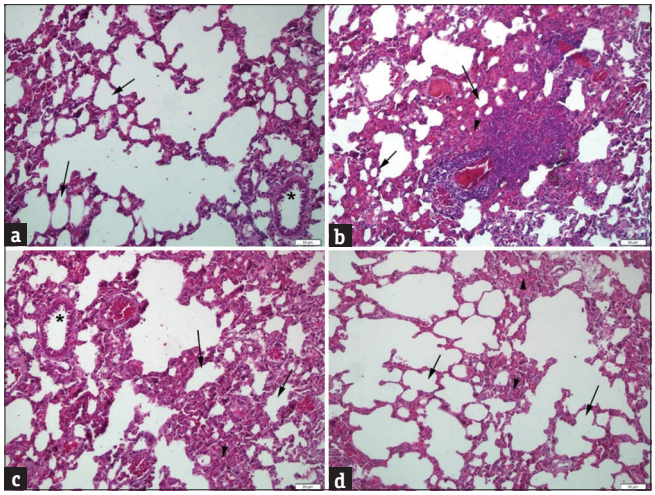

Figure 3: Microscopic examination of lung tissues. (a) Sham group: regular alveolar structure (arrows) and interstitial space, bronchiole (*); (b) carotid I/R group: severe and diffuse interstitial edema (arrowhead) and capillary obstruction in hemorrhagic areas and decreased alveolar spaces (arrows); (c) I/R + MESNA 75 mg/kg group: improved alveolar structures (arrows) by regression of the interstitial edema (arrowhead) and bronchioles (*); (d) I/R + MESNA 150 mg/kg group: recovery highlighted in alveolar structure (arrows) and reduced interstitial edema (arrowheads). (H.E, Bar 50 µm)

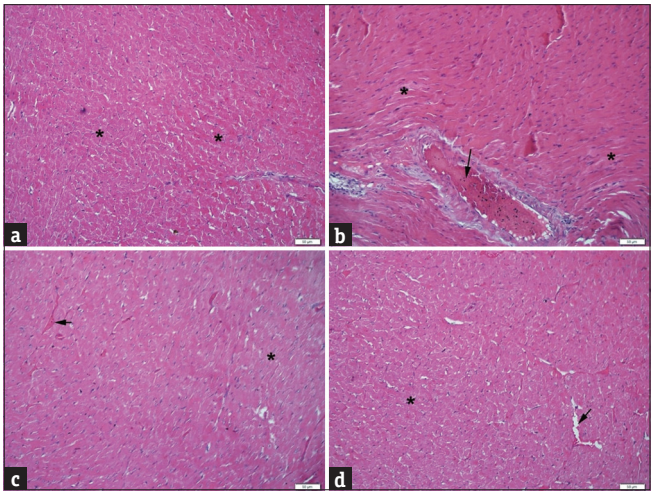

Figure 4: Microscopic examination of heart tissues. (a) sham group: regular arrangement of cardiomyocytes and capillaries (*); (b) carotid I/R group: severe congestion of the capillaries (arrow), cytoplasmic disorganization in cardiomyocytes (*); (c) I/R + MESNA 75 mg/kg group: reduced capillary congestion (arrowhead) and relative organization of cardiomyocytes (*); (d) I/R + MESNA 150 mg/kg group: marked regression of capillary congestion (arrow) and regular pattern of cardiomyocytes (*). (H.E, Bar 50 µm)

these changes caused by MESNA 75 and 150 mg/kg were not significantly different when both groups were compared (P > 0.05) [Table 5].

Lung morphometric result

Lung congestion, alveolar degeneration, and interstitial edema scores were significantly higher in the carotid I/R group than in the sham group (P < 0.0001). Treatment with MESNA (75 mg/kg and 150 mg/kg) significantly decreased the values of lung histological features compared with the sham and carotid I/R groups (P < 0.0001). In addition, alveolar degeneration and interstitial edema scores were more significantly decreased with MESNA 150 mg/kg than with MESNA 75 mg/kg (P < 0.01) [Table 6].

Heart morphometric result

Heart congestion, cardiomyocyte degeneration, and inflammation scores were significantly higher in the carotid I/R group than in the sham group (P < 0.0001). Treatment with MESNA especially high dose (150 mg/kg) decreased heart histological feature scores compared with the sham and carotid I/R groups (P < 0.05–0.0001). In addition, cardiomyocyte degeneration scores were significantly decreased more with MESNA 150 mg/kg than with MESNA 75 mg/kg (P < 0.01) [Table 7].

Microscopic presentation of lungs, heart, and brain sections from the treated groups

Light microscopy examination of lung tissue in the sham group showed a consistent alveolar structure

and interstitial space [Figure 3a]. In the carotid IR group, diffuse and severe hemorrhage with edema in interstitial spaces was observed. Besides, distended alveolar walls and decreased alveolar space due to edema as well as severe leukocytes accumulation were observed [Figure 3b]. In IR + MESNA 75 mg/kg group, due to the regression of hemorrhage in the interstitial space, an improvement in alveolar structure and a decrease in leukocyte accumulation were observed [Figure 3c]. In the I/R + MESNA 150 mg/kg group, the alveolar structure regenerated besides regression of interstitial edema [Figure 3d].

Light microscopy examination of heart tissue in the sham group showed a regular arrangement of cardiomyocytes and numerous capillaries [Figure 4a]. In the carotid IR group, remarkable interstitial edema and congestion in the capillaries and prominent perinuclear and cytoplasmic disorganization in the cardiomyocytes were observed [Figure 4b]. In the IR + MESNA 75 mg/kg group, the general cardiac morphology showed a decrease in interstitial edema and congestion in capillaries and regeneration of cardiomyocytes [Figure 4c]. In the I/R + MESNA 150 mg/kg group, congestion was markedly reduced and regular cardiomyocytes were prominent [Figure 4d].

Light microscopy examination of brain tissue in the sham group revealed regular morphology of neurons and neuropils in the cortex [Figure 2a]. However, the carotid I/R group [Figure 2b] showed degenerated neurons with marked shrinkage of the nucleus and cytoplasm. The I/R + MESNA 75 mg/kg group showed less neuronal degeneration compared with the carotid I/R group [Figure 2c]. The I/R + MESNA 150 mg/kg group showed regeneration of neuropil morphology [Figure 2d].

Discussion

Occlusion of the carotid artery triggers cerebral ischemia, causing significant local tissue damage. The heart and lungs are two distant organs that are susceptible to the adverse effects of carotid ischemia-reperfusion.[1,23] Therefore, the aim of the present study was to investigate the effects of MESNA on local and distant organ damage caused by carotid ischemia-reperfusion (I/R) by assessing the proinflammatory cytokines and proteolytic enzyme pathways.

The carotid artery is occluded in experimental studies to induce ischemia because it is a widely accepted experimental model for ischemia-reperfusion that mimics the characteristics of acute cerebrovascular injury in humans.[1,21] The current data show that carotid I/R causes a significant increase in serum levels of proteolytic enzymes as well as proinflammatory cytokines, resulting in damage to brain, heart, and lung tissue.

Lipid peroxidation caused by oxidative degradation of polyunsaturated fatty acids in membranes is thought to play a key role in disrupting cell membrane integrity and cell lysis.[4] In the present study, MDA levels, a product of lipid peroxidation,[24,25] were found to be significantly elevated in serum as a result of carotid I/R. High MDA levels may indicate an increase in lipid peroxidation, which can lead to oxidative tissue injury due to intense free radical attack.[25,26] Our results showed that MESNA (75 and 150 mg/kg) significantly decreased the I/R-induced high serum MDA level to a comparable control level, as reported in previous studies.[4,8,27] Thus, MESNA may protect against carotid ischemia-reperfusion-induced oxidative tissue damage by maintaining cell membrane integrity.

In the current study, carotid I/R significantly altered serum levels of AST, ALP, ALT, and LDH. Alteration in serum enzyme levels is indicative of organ dysfunction.[8,25,28,29] MESNA (75 and 150 mg/kg) significantly reversed the carotid I/R-induced increase in serum enzyme levels. This decrease in serum enzyme levels after MESNA treatment could be attributed to the ability of MESNA to prevent the leakage of intracellular enzymes from damaged cells by promoting cell regeneration and tissue repair. Our results are consistent with previous studies on the protective effects of intraperitoneally administered MESNA.[30,31]

The role of proinflammatory cytokines in 1/R-induced tissue injury has been described in several previous studies.[5,8,32] In this study, we investigated the effect of MESNA on the serum concentration of TNF-α and IL-1β, which are cytokines with different biological functions, especially in inflammatory and immune responses. These proinflammatory cytokines serve as systemic markers of tissue injury.[33] In our study, carotid artery I/R triggered a significant increase in serum levels of TNF-α and IL-1β, which was consistent with the results of previous studies that reported that carotid artery I/R increased serum levels of proinflammatory cytokines.[5,32] Increased serum levels of TNF-α and IL-1β indicate infiltration of inflammatory cells into the injured tissue and increased cytokine production, leading to local exacerbation of injury and spread of inflammation to distant organs.[34] MESNA (75 and 150 mg/kg) reversed the I/R-induced increase in serum TNF-α and IL-1β, and histopathological results revealed that tissue damage was significantly prevented. These results are consistent with the previous studies.[31,35] The ability of MESNA to regulate the

inflammatory process in ischemia-reperfusion could be through several mechanisms, including downregulation of nuclear factor-κB (NF-κB) activity,[36,37] inhibition of myeloperoxidase and inducible nitric oxide,[36,38] and monocyte chemotactic protein-1, which regulates the migration and infiltration of proinflammatory proteins.[39,40]

Matrix metalloproteinases and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), play an important role in inflammation-induced tissue damage and subsequent remodeling to maintain tissue homeostasis.[41] Increased serum MMPs and/or TIMPs levels have been detected in humans and animals with various inflammatory diseases because the production of these enzymes and their inhibitors is modulated by proinflammatory mediators.[25,42,43]

The activity of MMPs depends on the balance between the concentration of active enzyme and the TIMPs.[44] MESNA has been reported to affect the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[12] MMPs degrade the extracellular matrix (ECM), while TIMP-1, which are overexpressed in certain tissues such as brain,[45] heart,[46] and lung,[47] inhibit MMP activity and help maintain the integrity of the ECM.[41] A decrease in TIMP levels may lead to an increase in MMP activity, resulting in increased degradation of the ECM and potentially exacerbating tissue damage. In the present study, MESNA (75 and 150 mg/kg) suppressed the carotid I/R-induced increase in serum MMP (-1, -2, -8) levels and increased serum TIMP-1 levels compared with the sham group, thus promoting ECM stability and attenuating tissue damage, as shown by histopathological results. This effect may contribute to the protective mechanism of MESNA against carotid ischemia-reperfusion injury.

Conclusion

We assessed the extent of tissue damage caused by carotid ischemia-reperfusion with emphasis on brain, lung, and heart. According to the study results, brain neuronal degeneration, lung congestion, alveolar degeneration, interstitial edema, cardiac congestion, and cardiomyocyte degeneration were significantly reduced by MESNA especially at the high dose, indicating a possible dose-dependent effect. These histopathological observations support our biochemical findings that MESNA (75 and 150 mg/kg) protects brain, lung, and heart tissues from carotid ischemia-reperfusion-induced injury by preventing oxidative damage due to buildup of free radicals, infiltration of inflammatory mediators, and maintenance cell membrane stability.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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