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Correction Article
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THE PROTECTIVE ROLE OF CARNOSINE IN LUNG INJURY FOLLOWING SINGLE LUNG VENTILATION

Tek Akciğer Ventilasyonu Sonrası Oluşan Akciğer Hasarı Üzerine Karnozin'in Koruyucu Rolü

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ABSTRACT

Objective: The aim of this study is to investigate the protective effect of carnosine on lung injury after single lung ventilation in a rat model.

Material and Methods: Twenty Sprague-Dawley rats were divided into two groups for the study (n=10). We used single lung ventilation (SLV) for 60 minutes, following a 30-minute dual lung ventilation (DLV) model on all animals. In the carnosine group, animals received 250 mg/kg carnosine intraperitoneally 10 minutes before the start of the experiment and the control group was injected with the same amount of saline solution. Lung samples from the control and carnosine groups were obtained for biochemical analysis and histopathological evaluation at the end of SLV and DLV. Tissue levels of superoxide dismutase (SOD), malondialdehyde (MDA), and tumor necrosis factor-alpha (TNF-α) were measured. Histopathologically, hematoxylin-eosin-stained tissues were scored for lung injury parameters such as alveolar congestion, intra-alveolar hemorrhage, presence and amount of leukocyte and lymphocyte infiltration.

Results: In the carnosine group, TNF-α levels were significantly reduced compared to the control group at the end of SLV and DLV ($p<0.05$). However, there was no significant difference in MDA and SOD levels between the two groups after SLV and DLV ($p>0.05$). Histopathological evaluation showed a statistically significant reduction in polymorphonuclear leukocyte (PMNL) and lymphocyte infiltration in the carnosinegroup ($p<0.05$).

Conclusion: We believe that carnosine has the potential for preventing injury caused by SLV in thoracic surgery procedures.

Keywords: *Single lung ventilation, carnosine, MDA, TNF-α, SOD, alveolar congestion, lymphocyte infiltration*

ÖZ

Amaç: Bu çalışmanın amacı, sıçanlarda tek akciğer ventilasyonu sonrasında oluşan akciğer hasarı üzerine karnozininin koruyucu etkisini araştırmaktır.

Gereç ve Yöntemler: Çalışma için 20 adet *Sprague Dawley* cinsi sıçan, eşit sayıda (n=10) iki gruba ayrılarak 60 dakika boyunca tek akciğer ventilasyonu (TAV) sonrasında 30 dakika süreyle çift akciğer ventilasyonu (ÇAV) uygulandı. Karnozin grubundaki sıçanlara deneye başlamadan 10 dakika önce 250mg/kg dozunda intraperitoneal karnozin enjeksiyonu, kontrol grubuna ise aynı miktarda serum fizyolojik enjeksiyonu yapıldı. Her iki gruptanda TAV ve ÇAV sonunda biyokimyasal analiz ve histopatolojik inceleme için akciğer doku örnekleri alındı. Biyokimyasal analizde doku superoksid dismutaz (SOD), malondialdehit (MDA) ve tümör nekroz faktör alfa (TNF-α) düzeyleri ölçüldü. Histopatolojik incelemede dokular hemotoksilen eosin ile boyandı ve akciğer hasar parametreleri, alveolar konjesyon, intraalveoler kanama, lökosit ve lenfosit infiltrasyonu varlığı ve miktarı ile skorlandı.

Bulgular: Karnozin uygulanan grupta, TAV ve ÇAV sonunda TNF-α düzeylerinde kontrol grubuna kıyasla istatistiksel olarak anlamlı bir azalma saptandı ($p<0,05$). Ancak her iki grupta da TAV ve ÇAV sonrası MDA ve SOD değerlerinde anlamlı bir farklılık görülmedi($p>0,05$). Histopatolojik değerlendirmede, karnozin uygulanan grupta polimorfonükleer lökosit (PMNL) ve lenfosit infiltrasyonunun istatiksel olarak anlamlı düzeyde azaldığı görüldü ($p<0,05$).

Sonuç: Göğüs cerrahisi uygulamalarında, TAV'a bağlı akciğer hasarının önlenmesinde karnozin kullanımının potansiyel bir terapötik ajan olabileceğini düşünüyoruz.

Anahtar Kelimeler: *Tek akciğer ventilasyonu, karnozin, MDA, SOD, TNF-α, alveoler konjesyon, lenfosit infiltrasyonu*

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INTRODUCTION

Single-lung ventilation (SLV) is a technique often used in thoracic surgery to facilitate the surgical procedure.[1] One of the most important physiological changes occuring during SLV is hypoxemia due to the redistribution of pulmonary and bronchial artery flows of the collapsed lung and opening of the intrapulmonary shunts. With the termination of SLV, blood flow to the ischemic lung is restored and reperfusion occurs.[1,2] During reperfusion, free oxygen radicals (FORs) are produced when molecular oxygen re-enters the cell.[3,4] Excessive production of free radicals or insufficient antioxidant defense mechanisms results in damage to the biomolecules and tissue components. The unsaturated bonds of cholesterol and fatty acids in the cell membranes readily react with free radicals, forming peroxidation products such as malondialdehyde (MDA), which can diffuse to distant cells.[4] Additionally, the inflammatory response initiated during reperfusion activates the immune and coagulation systems, leading to endothelial dysfunction and apoptotic cell death.[3]

Carnosine (CAR) is a multifunctional dipeptide composed of endogenously synthesized beta-alanine and L-histidine.[5] While many antioxidants aim to prevent free radicals from entering tissues, these mechanisms may become ineffective once the initial defense is compromised. CAR not only inhibits the formation of free radicals but also provides an effective defense against toxic compounds generated by free radical reactions. Consequently, it protects tissues from secondary oxidative damage.[6] In addition to its antioxidant properties, several studies have demonstrated that CAR increases interleukin-1 synthesis, suppresses apoptosis, activates B and T lymphocytes, exerts a protective effect on erythrocyte membranes, and reduces inflammation. Due to its anti-inflammatory, antineoplastic, immunomodulatory, and neuroprotective effects, CAR has been clinically utilized in the treatment of polyarthritis, gastric and duodenal ulcers, essential hypertension, and ischemic heart disease.[7] However, studies investigating the effects of CAR on pulmonary function are limited. In this study, we aimed to evaluate the protective effects of CAR against lung injury following SLV, a procedure commonly performed in thoracic surgery, based on its well-documented antioxidant and anti-inflammatory properties.

MATERIALS AND METHODS

This study was approved by the Local Ethics Committee for Animal Experiments of Eskişehir Osmangazi University Faculty of Medicine on December 28, 2012, with protocol number 306/2012, and was conducted in accordance with the Declaration of Helsinki. All animals were obtained from the Medical and Surgical Experimental Research Center. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and good clinical practice.

A total of 20 Sprague-Dawley rats (both male and female), weighing between 250 and 370 grams, were randomly assigned to two equal groups (n=10). All animals were housed in an automatically controlled environment with a 12-hour light-dark cycle, a temperature of 20-22 °C, and a humidity level of 45%-50%. All animals were kept in transparent cages on a standard rat chow diet and given tap water.

Preparation of the subject and surgical technique

A total of 20 Sprague-Dawley rats were randomly assigned to two groups: the control group (n=10) and the carnosine-treated group (n=10). The sample size was determined based on previous similar experimental studies investigating ischemia-reperfusion injury models in rodents. Although no formal power analysis was conducted due to the exploratory nature of the study, a group size of 10 animals was considered sufficient to observe meaningful biochemical and histopathological differences. A larger sample might have increased the statistical power, but ethical considerations regarding animal use and feasibility constraints limited the sample to 20 animals.

Food was withdrawn (except for water) 8 hours before the experiment. Under anaesthesia with intraperitoneal 40 mg/kg ketamine (Eczacıbaşı Pharmaceuticals Inc., Lüleburgaz, Türkiye) and 5 mg/kg xylazine (Provet Veterinary Products Istanbul, Türkiye) per body weight was recorded, and additional doses of anesthetic were administered during the experiment when necessary. To maintain hemodynamic stability, 10 ml/kg of 0.9% NaCl solution was administered, and to prevent thromboembolic complications, 100 U/kg heparin (Nevparin 25,000 IU/5 ml vial, Mustafa Nevzat) was injected intraperitoneally. Electrocardiographic monitoring was performed, and blood pressure was measured noninvasively via the tail.

Following anesthesia, rats were placed in the supine position, and a tracheostomy was performed. A 16G cannula was inserted into the trachea and advanced selectively into the right main bronchus to enable left-lung collapse and ensure single-lung ventilation (SLV) of the right lung only. Correct placement was confirmed via auscultation and observation of unilateral chest rise (right lung only). The cannula was secured in place, and the animals were ventilated using a ventilator (Rodent Ventilator 7025, Hugo Sachs Electronics, Germany) with the following parameters: tidal volume 6 ml/kg, respiratory rate 80 breaths/min, and FiO_2 1.0.

After 60 minutes of SLV, the cannula was gently

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withdrawn to the carinal level, and bilateral ventilation (DLV) was initiated with adjusted settings (tidal volume 8 ml/kg, respiratory rate 60 breaths/min). DLV was maintained for an additional 30 minutes. At the end of SLV, a left thoracotomy was performed and the left lung (collapsed/ischemic side) was partially resected to obtain tissue samples. After the DLV period, remaining lung tissue from the left side was harvested for further analysis. In this setup, the right lung was continuously ventilated, while the left lung was kept non-ventilated during SLV, mimicking the clinical scenario of SLV in thoracic surgery. The left lung (ischemic/reperfused) was selected for histopathological and biochemical analyses, as it was subject to the ischemia-reperfusion sequence.

In the carnosine group, carnosine (L-carnosine, Sigma-Aldrich, CAS No: 305-84-0) was administered intraperitoneally at a dose of 250 mg/kg, 15 minutes prior to the surgical intervention whereas the control group only received the same amount of fluid. At the end of the experiment, all subjects were humanely euthanized under deep anesthesia to ensure the absence of pain or distress.

A part of the tissue samples obtained following SLV and DLV were preserved in 10% neutral buffered formalin solution for histopathologic analysis, while the remaining samples were stored in -80 °C in liquid nitrogen for biochemical assessments, including SOD activity (Superoxide Dismutase Assay Kit - Item No: 706002 - Cayman Chemical Company, Ann Arbor, MI, USA), MDA levels (TBARS Assay Kit - Item No: 10009055 - Cayman Chemical Company, Ann Arbor, MI, USA), and TNF-α concentrations (RAT TNF-α ELISA KIT - KRC3011 - Invitrogen Corporation 542 Flynn Road, Camarillo, CA 93012, USA).

For histopathological examination, paraffin-embedded tissue blocks were prepared. 4-µm sections were obtained using a microtome and subsequently stained with hematoxylin and eosin (H&E). Histopathological evaluation was conducted by a single pathologist blinded to the study groups. The assessments were performed using a light microscope, with at least two different sections from each sample analyzed. Lung tissue damage was scored at 10×, 20×, and 40× magnifications based on the presence and amount of alveolar congestion, PMNL infiltration, lymphocyte infiltration, intra-alveolar hemorrhage, and interstitial edema. The scoring system was as follows: (0) No change; (1) Focal minimal change; (2) Multifocal moderate change; (3) Multifocal severe change

Statistical analysis

Statistical analyses were performed using Minitab 16 (Minitab Inc., State College, PA, USA) and IBM SPSS 21.0 (IBM Corp., Armonk, NY, USA). Data were analyzed using Student's *t*-test. Results were expressed as mean ± standard deviation (SD). Comparisons between groups and procedures were conducted using a two-way analysis of variance (ANOVA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Biochemical analysis

MDA levels

MDA levels were evaluated following SLV and DLV in both of the control and carnosine groups. The mean MDA levels were lower in the carnosine group at the end of SLV, compared to the control group, however, this difference did not reach statistical significance (p>0.05) (Table 1).

Table 1: MDA, SOD, and TNF-a measurements at study time points

	Control (n:10)	Carnosine (n:10)	P
MDA (µM)			
End of SLV (60 min) Mean±SD	3.0385±0.9549	2.8509±1.2908	p>0.05
End of DLV (30 min) Mean±SD	3.0981±0.9692	3.2008±1.0284	p>0.05
P	p>0.05	p>0.05	
SOD (U/mL)			
End of SLV (60 min) Mean±SD	1.1170±0.4517	0.934±0.387	p>0.05
End of DLV (30 min) Mean±SD	0.8356±0,4386	0.8254±0,3301	p>0.05
P	p>0.05	p>0.05	
TNF-α (pg/mL)			
End of SLV (60 min) Mean±SD	65.49±16,99	76.83±19.14	p>0.05
End of DLV (30 min) Mean±SD	79.20±29.37	23.21±12.82	p<0.001
p	p>0.05	p<0.001	

DLV: Double lung ventilation; MDA: Malondialdeyhde; SD: Standart deviation; SLV: Single lung ventilation; SOD: superoxside dismutase; TNF-α: Tumor necrosis factor alpha; p<0.05 is significant value.

SOD levels

The mean SOD levels were lower in the carnosine group compared to the control group at the end of both ventilation periods, but it didn't reach statistical significance (p>0.05). Additionally, in the carnosine group the mean SOD levels were higher at the end of SLV compared to the level at the end of DLV, but the difference was not statistically significant (Table 1).

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TNF-α levels

In the carnosine group the mean TNF-α level significantly decreased at the end of DLV compared to the level at the end of SLV (76.83±19.14 vs. 23.21±12.82 pg/mL, p<0.001). A decrease was also observed in the control group after DLV, but this did not reach statistical significance. Similarly at the end of the DLV, the mean TNF-α level was significantly lower in the carnosine group compared to the control group (79.20±29.37 vs. 23.21±12.82 pg/mL, p<0.001) and this difference was statistically significant (Table 1).

Histopathologic Examination

All lung samples were comprehensively evaluated on the presence and amount of alveolar congestion, interstitial edema, intra-alveolar hemorrhage, polymorphonuclear leukocyte infiltration (PMNL), and lymphocyte infiltration. Although there was a decrease in alveolar congestion, interstitial edema and intra alveolar hemorrhage parameter, after DLV in both groups, no statistical difference was detected. In the carnosine group, a statistically significant reduction in PMNL and lymphocyte infiltration parameter values were observed at the end of both DLV and SLV compared to the control group (p<0.05) (Figures 1 and 2).

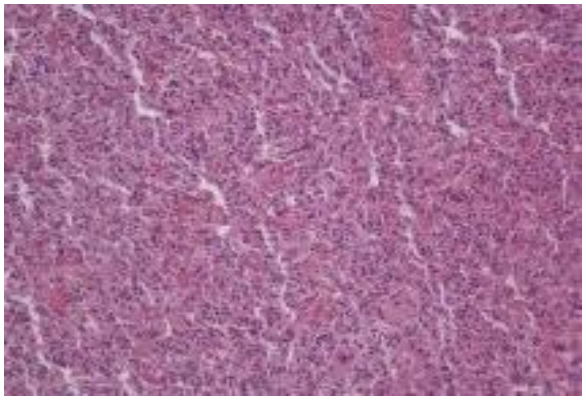

Figure 1: Increased interstitial edema, congestion, intraalveolar hemorrhage, and PMNL and lymphocyte infiltration in the interstitial lung parenchyma in the control group at the end of DLV. (H&Ex20**)**

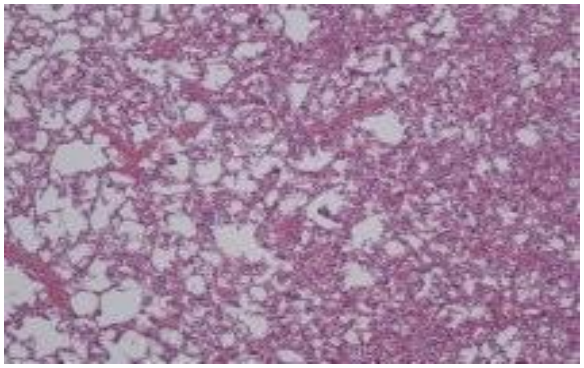

Figure 2: Areas of partially regressed interstitial edema, congestion, intraalveolar hemorrhage and PMNL and interstitial lymphocyte infiltration in the carnosine group at the end of DLV compared with the control group at the end of DLV. (H&Ex20)

DISCUSSION

Single-lung ventilation (SLV) is a commonly used technique to optimize the surgical field and manipulation in thoracic surgery.[1] However, ischemia-reperfusion (I/R) injury secondary to the SLV may lead to various pathological changes in lung tissue through the mechanisms of oxidative stress and inflammatory responses.[1,2] Research has indicated that extended SLV duration leads to lung damage due to oxidative stress, as evidenced by histological and biochemical tests.[8-10] In a study by Mithos et al., 212 cancer patients were prospectively evaluated perioperatively, and it was shown that lung re-expansion induced severe oxidative stress and increased the production of free radicals (FOR). The same study reported that lung cancer patients produced more FOR than the normal population.[11]

Markers of oxidative stress, such as superoxide radicals (SORs) and malondialdehyde (MDA), which are generated in lung tissue during ischemia-reperfusion (I/R) injury, promote lipid peroxidation, leading to endothelial dysfunction and apoptosis.[3,4] Furthermore, the increase in pro-inflammatory cytokines such as TNF-α exacerbates the inflammatory response.[12]

Carnosine is an endogenously synthesized dipeptide present in high concentrations in the brain, kidneys, heart, and skeletal muscle. Studies have demonstrated that it protects cell membranes from lipid peroxidation by neutralizing superoxide radicals (SORs), particularly malondialdehyde (MDA), through its antioxidant properties.[6] Furthermore, Stvolinsky et al. showed that carnosine significantly increased survival time in rats with global brain ischemia induced by carotid artery occlusion. This effect was associated with an increase in Na/K-ATPase and monoamine oxidase B enzyme activities, in addition to the antioxidant effects of carnosine.[13] Nicoletti et al. found that carnosine directly interacted with nitric oxide (NO) in rat Astro-glial cell cultures and significantly protected against the cytotoxic effects of NO.[14]

Carnosine reduces inflammation, enhances interleukin-1 production, suppresses apoptosis, and activates B and T lymphocytes.[13] Baykara et al. found that carnosine, administered at a dose of 250 mg/kg prior to ischemia and after reperfusion, histopathologically ameliorated liver injury, increased glutathione (GSH) levels, and decreased myeloperoxidase enzyme activity in a liver injury model induced by ischemia-reperfusion (I/R).[15] In the I/R model created by clamping the abdominal aorta, it was reported that carnosine administered 10 minutes prior to reperfusion reduced levels of malondialdehyde (MDA) and oxidized glutathione, with decreased immunoreactivity. While significant reductions in MDA and SOD levels have been reported in the literature for carnosine-treated groups, no similar

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changes were observed in the end-SLV and end-DLV levels in both groups in our study. TNF-α is a molecule synthesized and secreted by mononuclear phagocytes and T lymphocytes during inflammation, serving as a key indicator of tissue inflammation. The literature reports an increase in TNF-α levels in lung injury following mechanical ventilation. Furthermore, it has been observed that carnosine significantly reduces the levels of pro-inflammatory molecules, such as TNF-α, IL-6, IL-10, and monocyte chemoattractant protein, which are elevated in acetaminophen-induced liver injury. These findings suggest that carnosine is a potent anti-inflammatory agent.[12] In our study, a significant reduction in TNF-α levels was noted at the end of SLV and DLV in the carnosine group. This finding biochemically substantiates that carnosine has a potent anti-inflammatory effect after SLV, consistent with data in the literature. Reperfusion of ischemic tissue results in the disruption of endothelium-dependent vasodilation in arterioles, formation of capillary leukocyte plugs, increased fluid filtration, and leakage of plasma proteins from postcapillary venules, ultimately leading to disruption of microvascular function.

In the lungs, ischemia-reperfusion (I/R) injury is mediated by lymphocytes, pulmonary arterial endothelial cells, alveolar macrophages, and pulmonary alveolar type II cells.[16] In our study, a significant reduction in polymorphonuclear leukocyte (PMNL) and lymphocyte infiltration wereobserved in the carnosine-treated group. Given that TNF-α is a molecule synthesized and released by lymphocytes and serves as a key marker of tissue inflammation, the histopathological findings and biochemical TNF-α parameters were found to be consistent.

Considering studies that show MDA levels increase with prolonged SLV time, MDA levels remained stable in our study, and the antioxidant effect of carnosine could not be detected. This may be due to the 60-minute SLV duration in our study being insufficient to induce oxidative stress. Nonetheless, we assert that the protective effect of carnosine against SLV-induced lung injury could be evidenced in additional investigations with a prolonged SLV duration.

This study has several limitations. First, the sample size was limited to 20 rats. Although similar numbers have been used in previous experimental models, a larger sample size could have increased the statistical power and potentially revealed subtle differences in biochemical parameters. Second, only a single dose (250 mg/kg) and timing (15 minutes before surgery) of carnosine administration were evaluated. The optimal therapeutic range of carnosine could not be determined, as other doses or administration schedules were not investigated. Third, the ischemia-reperfusion model in this study was of short duration, with single-lung ventilation limited to 60 minutes. Longer durations may induce more pronounced oxidative stress and histopathological changes. Finally, this study was conducted on an animal model, and the direct generalizability of the results to humans is limited. Further preclinical and clinical studies are required to validate the therapeutic potential of carnosine in thoracic surgery settings.

In this experimental model of single-lung ventilation, carnosine demonstrated a significant anti-inflammatory effect, as evidenced by the reduction in TNF-α levels and histopathological attenuation of polymorphonuclear leukocyte and lymphocyte infiltration. Although no significant differences were observed in oxidative stress markers such as MDA and SOD, the anti-inflammatory properties of carnosine appear to play a central role in mitigating lung injury. The absence of changes in oxidative stress parameters may be related to the limited duration of the SLV period. These findings suggest that carnosine may be a promising therapeutic agent for reducing lung injury associated with SLV, particularly in prolonged or high-risk thoracic surgery cases. Further studies with larger sample sizes and extended ischemia durations are warranted to validate these results and better to understand the underlying mechanisms of carnosine's protective effects.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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