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Protective effects of melatonin on lung damage associated with one-lung ventilation: An experimental study

Melatoninin tek akciğer ventilasyonuna bağlı akciğer hasarı üzerine koruyucu etkisi: Deneysel çalışma

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ABSTRACT

Background: This study aims to investigate the protective effect of melatonin on lung damage induced by one-lung ventilation in a rat model.

Methods: A total of 20 healthy, Sprague-Dawley male rats were randomized into two equal groups as control (n=10) and melatonin groups (n=10). The control group underwent 60 min of one-lung ventilation, followed by 30 min of two-lung ventilation. In the melatonin group, the rats were administered 10 mg/kg melatonin intraperitoneally 10 min before the start of the experiment. At the end of both ventilation periods, tissue samples were obtained from the lungs of the control and melatonin groups for biochemical analysis and histopathological examinations. Tissue superoxide dismutase, malondialdehyde, and tumor necrosis factor-alpha levels were measured. Lung tissue samples were examined based on the presence and amount of alveolar congestion, intra-alveolar bleeding, and leukocyte and lymphocyte infiltration.

Results: At the end of the study, lung tissue malondialdehyde (3.8±0.9 vs. 1.8±0.8 μM; p<0.001) and tumor necrosis factor-alpha levels (47.2±15.0 vs. 21.8±7.2 pg/mL; p<0.001) of the melatonin group were found to significantly decrease, compared to the control group. Superoxide dismutase levels of the melatonin group increased at the end of both ventilation periods, and the increase at the end of one-lung ventilation was found to be statistically significant (0.6±0.2 vs. 1.3±0.7 U/mL; p<0.05). Histopathological examination demonstrated that the tissue damage was less in the melatonin group. There was a significant decrease in the alveolar congestion in this group (p=0.0401). Although other histopathological parameters decreased in the melatonin group, no significant difference was found.

Conclusion: Our study results demonstrate that melatonin has protective effects on the lung damage induced by one-lung ventilation both at biochemical and histopathological levels in rats.

Keywords: Histopathology, malondialdehyde, melatonin, one-lung ventilation, superoxide dismutase, tumor necrosis factor-alpha.

ÖZ

Amaç: Bu çalışmada sıçan modelinde tek akciğer ventilasyonuna bağlı akciğer hasarı üzerine melatoninin koruyucu etkisi araştırıldı.

Çalışma planı: Toplam 20 adet Sprague-Dawley cinsi sağlıklı erkek sıçan kontrol (n=10) ve melatonin (n=10) grubu olmak üzere iki eşit gruba randomize edildi. Kontrol grubuna 60 dk. süreyle tek akciğer ventilasyonunu takiben, 30 dk. süreyle çift akciğer ventilasyonu uygulandı. Melatonin grubundaki sıçanlara deneye başlamadan 10 dakika önce 10 mg/kg intraperitoneal melatonin verildi. Her iki ventilasyon süresinin sonunda biyokimyasal ve histopatolojik inceleme için kontrol ve melatonin gruplarından akciğer doku örnekleri alındı. Doku süperoksit dismutaz, malondialdehit ve tümör nekroz faktör-alfa düzeyleri ölçüldü. Akciğer doku örnekleri alveolar konjesyon, intraalveoler kanama, lökosit ve lenfosit infiltrasyonunun varlığı ve miktarı açısından değerlendirildi.

Bulgular: Çalışma sonunda, melatonin grubunda akciğer dokusunda malondialdehid (3.8±0.9'e kıyasla 1.8±0.8 μM; p<0.001) ve tümör nekroz faktör-alfa (47.2±15.0'e kıyasla 21.8±7.2 pg/mL; p<0.001) düzeyleri, kontrol grubuna kıyasla, anlamlı düzeyde düşük bulundu. Melatonin grubunun süperoksit dismutaz düzeyleri her iki ventilasyon süresi sonunda arttı ve tek akciğer ventilasyonunun sonundaki artış istatistiksel olarak anlamlı bulundu (0.6±0.2'ye kıyasla 1.3±0.7 U/mL; p<0.05). Histopatolojik incelemede melatonin grubunda doku hasarının daha az olduğu gözlendi. Bu grupta alveolar konjesyonda da anlamlı bir azalma görüldü (p=0.0401). Melatonin grubunda diğer histopatolojik parametreler azalmakla birlikte, anlamlı bir fark görülmedi.

Sonuç: Çalışma sonuçlarımız melatoninin sıçanlarda hem biyokimyasal hem de histopatolojik düzeyde tek akciğer ventilasyonunun neden olduğu akciğer hasarı üzerinde koruyucu etkilere sahip olduğunu göstermektedir.

Anahtar sözcükler: Histopatoloji, malondialdehid, melatonin, tek akciğer ventilasyonu, süperoksit dismutaz, tümör nekroz faktör-alfa.

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Mechanical ventilation itself may result in an injury even in healthy lungs.[1] Such patients are under the risk for a variety of complications due to problems related to oxygen toxicity, volutrauma, barotrauma, low cardiac output, and endotracheal tube insertion.[2,3]

One-lung ventilation (OLV) is a unique ventilation method which was first described by Gale and Waters in 1931.[4] The main goals of OLV are to improve exposure of surgical field and to protect the healthy lung by diversion of ventilation from the damaged lung or airway. Despite being one of the indispensable techniques for ventilation in thoracic surgery, it has the potential to cause more lung damage than the conventional ventilation techniques.[5] During OLV, the lung that is being operated remains atelectasic for a period of time, leading to hypoxic pulmonary vasoconstriction (HPV). This condition results in nearly 50% of a decline in the blood flow, causing ischemia in the lung tissue.[6] After the surgical procedure, with transition to two-lung ventilation (TLV), re-expansion allows for the entry of oxygen into the airways, followed by pulmonary vasodilatation and reperfusion of the lungs.[7] Reperfusion which develops after ischemia leads to the production of free oxygen radicals. Reperfusion also induces secretion of cytokines and causes changes in redox balance. In studies conducted with OLV, significant changes have been shown in biochemical markers such as superoxide dismutase (SOD), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, interleukin-1-beta (IL-1β), and IL-8 associated with lung damage, as well as histopathological changes.[4,8-10]

Melatonin is a hormone secreted by the pineal gland.[11] It is mainly responsible for the regulation of sleep, and it plays a role in different physiological conditions such as the regulation of endocrine rhythm, anti-gonadal activity, protection from free oxygen radicals, and neuroendocrine regulation of different immune functions.[12,13] Melatonin is both water- and lipid-soluble and, thus, can reach all the organelles of the cell including the nucleus. This characteristic renders melatonin superior in the protection of DNA from oxidative damage.[14,15]

Melatonin is a powerful antioxidant and has been shown to prevent the oxidative damage caused by lipid peroxidation.[16,17] Antioxidants show their effects via two pathways. The first is the provision of electrons to oxygen and nitrogen-based reactants independent of receptors, and the second is the ability to increase receptor bound SOD.[18-20] In the light of these data, it is not surprising that melatonin may result in certain alterations in redox balance in the lung tissue of rats undergoing OLV.

In the present study, we aimed to investigate the protective effect of melatonin on lung damage induced by OLV in a rat model.

MATERIALS AND METHODS

This experimental study was conducted at Eskişehir Osmangazi University Medical and Surgical Experimental Animals Application and Research Center between February 2013 and June 2013. The study protocol was approved by Eskisehir Osmangazi University, Animal Experiments Local Ethics Board (No. 54/307, Date: 28.12.2012). Laboratory animals were supplied by the Medical and Surgical Experimental Animals Application and Research Center. A total of 20 healthy, Sprague-Dawley male rats with a mean weight of 234 to 360 g were randomized into two equal groups as control (n=10) and melatonin groups (n=10). Throughout the study, the rats were kept in transparent cages with exposure to 12-hour light-dark cycles at 20 to 22ºC at 45 to 50% humidity that were all automatically adjusted. The rats were fed with standard rat feed (pellet feed) and tap water.

Preparation of subjects and surgical procedure

Anesthesia was administered in the form of ketamine at 40 mg/kg (Eczacıbaşı Pharmaceuticals Inc., Lüleburgaz, Turkey) and xylazine at 5 mg/kg (Provet Veterinary Products Istanbul, Turkey) via intraperitoneal route. Additional doses were administered, when needed. Blood pressures were monitored throughout the procedure in a non-invasive manner from their tails and electrocardiographic monitorization was also performed for all subjects. For the purpose of fluid resuscitation, all rats received 10 mL/kg 0.9% sodium chloride and 100 U/kg heparin for anticoagulation (Nevparin 25000 IU 5 mL flacon, Mustafa Nevzat Pharmaceuticals Inc., Istanbul, Turkey) intraperitoneally throughout the experiment.

Following anesthesia, the rats in the control group were placed in a supine position. Following surgical site cleansing with 10% povidone iodine, tracheostomy was performed. A 16-gauge branule was introduced into the trachea through the tracheostomy and advanced into the left main bronchus. One-lung ventilation was confirmed with inspection and auscultation. After confirming OLV, the branule was fixated to the left main bronchus. For 60 min, OLV was in place ensuring a tidal volume of 6 mL/kg, respiratory frequency of 80/min, and fraction of inspired oxygen (FiO_2) of 1.0 (Rodent Ventilator 7025, Hugo-Sachs Electronics,

March, Germany). Then, right hemithorax was entered via right thoracotomy and atelectasis of the right lung was confirmed. Right accessory lobes of the rats were removed and divided into two pieces for histopathological and biochemical examination. Half of the samples were stored in 10% formaldehyde solution for histopathological examination. The remaining parts of the lungs were frozen at -80ºC in liquid nitrogen and stored for SOD (Cayman's Superoxide Dismutase Assay Kit, Cayman Chemical, MI, USA), MDA (Cayman's TBARS Assay Kit, Cayman Chemical, MI, USA), and TNF-α (TNF-α (mouse) Enzyme-Linked Immunosorbent Assay Kit, Cayman Chemical, MI, USA) measurements.

At the end of OLV and after the completion of sampling procedure, the branule within the left main bronchus was retrieved above the carina and TLV was initiated. The procedure was continued for 30 min with a tidal volume of 8 mL/kg, respiratory frequency of 60/min, and FiO_2 of 1.0. At the end of TLV, the remaining right lung tissues were removed for sampling and divided into two and stored as described above.

During histopathological examination, lung tissue samples were stained with hematoxylin-eosin. The damage in the lungs was evaluated at 10×, 20×, and 40× magnifications and scored based on the presence and amount of alveolar congestion, polymorphonuclear leukocyte (PMNL) infiltration, lymphocyte infiltration, and intra-alveolar bleeding. All parameters were scored separately using the following scoring system: 0: No change, 1: Focal minimal change, 2: Multifocal moderate change, 3: Multifocal severe degree change.[21]

For the rats in the melatonin group, in addition to the procedure detailed above, 10 mg/kg melatonin (Melatonin, Sigma Chemical Co., MO, USA) was administered intraperitoneally 15 min before the procedure. At the end of the study, all rats were sacrificed under high-dose anesthesia.

Statistical analysis

Statistical analysis was performed using the Minitab version 16.0 (Minitab Inc., State College, PA, USA) and IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max). The Student's t-test was used to analyze biochemical data. The Wilcoxon test was used to analyze dependent groups (OLV control group - TLV control group, OLV melatonin group - TLV melatonin group) and Mann-Whitney U test was used to analyze independent groups (OLV control group - OLV melatonin group, TLV control group - TLV melatonin group) for histopathological examination. A p value of <0.05 was considered statistically significant.

RESULTS

Biochemical analysis

MDA levels

The mean MDA level was found to significantly decrease in the control group at the end of TLV (5.4±1.1 vs. 3.8±0.9 μM, respectively; p=0.002).

Table 1. MDA, SOD, and TNF-α measurements at study time points

	End of OLV (60 min)	End of TLV (90 min)	
Groups	Mean±SD	Mean±SD	*p*
MDA levels			
Control (n=10)	5.4±1.1	3.8± 0.9	0.002
Melatonin (n=10)	3.1±1.8	1.8±0.8	0.091
p	0.003	0.000112	
SOD levels			
Control (n=10)	0.6±0.2	0.4±0.1	0.017
Melatonin (n=10)	1.3±0.7	0.6±0.4	0.016
p	0.012	0.123	
TNF-α levels			
Control (n=10)	56.1±21.3	47.2±15.0	0.294
Melatonin (n=10)	24.5±6.1	21.8±7.2	0.402
p	0.001015	0.000354	

MDA: Malondialdehyde; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-alpha; OLV: One-lung ventilation; TLV: Two-lung ventilation; SD: Standard deviation; p<0.05 is significant value.

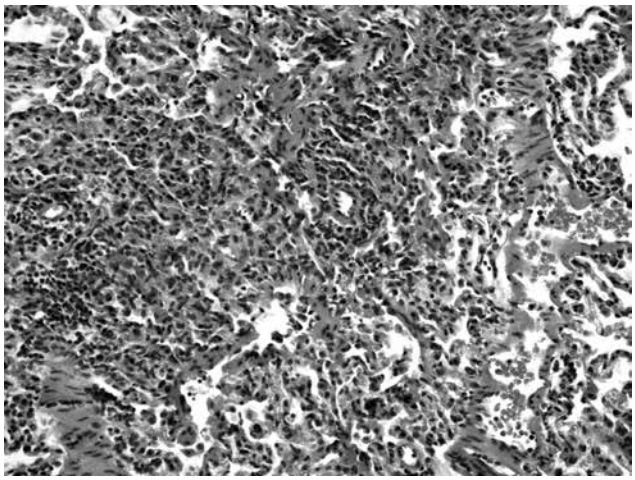

Figure 1. Severe congestion was detected in alveolar walls of rats in the control group. There was also increased intra-alveolar bleeding, leukocyte, and lymphocyte infiltration (H-E ×20).

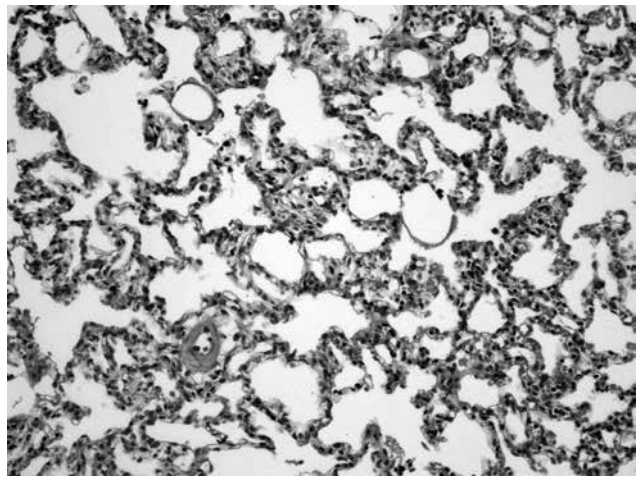

Figure 2. Minimal congestion was detected in alveolar wall in the melatonin group. There was also less intra-alveolar bleeding, leukocyte, and lymphocyte infiltration, compared to the control group (H-E ×20).

There was also a decrease in the melatonin group after TLV, but it did not reach statistical significance. The mean MDA levels were significantly lower in the melatonin group at the end of both ventilation periods, compared to the control group (at the end of OLV 5.4±1.1 vs. 3.1±1.8 μM, respectively; p=0.003 and at the end of TLV 3.8±0.9 vs. 1.8±0.8, respectively; p<0.001) (Table 1).

SOD levels

In the control group, the mean SOD level significantly decreased at the end of TLV, compared to the level at the end of OLV (0.6±0.2 vs. 0.4±0.1 U/mL, respectively; p=0.018). Similarly, the mean SOD level in the melatonin group at the end of TLV and it reached statistical significance, compared to the level at the end of OLV (1.3±0.7 vs. 0.6±0.4 U/mL; respectively; p=0.016).

The mean SOD level at the end of OLV was significantly higher in the melatonin group, compared to the control group (0.6±0.2 vs. 1.3±0.7 U/mL, respectively; p=0.012). Although the mean SOD level of the melatonin group was higher than the control group at the end of TLV, although the difference did not reach statistical significance (Table 1).

TNF-α levels

In both groups, there was no significant difference in the TNF-α levels at the end of OLV and TLV (Table 1). However, at the end of OLV, the mean TNF-α level was significantly lower in the melatonin group, compared to the control group (56.1±21.3 vs. 24.5±6.1 pg/mL, respectively; p=0.001015). On the other hand, the decrease was more significant at the end of TLV (47.2±15.0 vs. 21.8±7.2 pg/mL, respectively; p<0.001) (Table 1).

Histopathological examination

All lung tissue samples were evaluated based on the presence and amount of alveolar congestion, PMNL infiltration, lymphocyte infiltration, and intra-alveolar bleeding. Although all parameters decreased in the melatonin group, there was no significant difference between the groups at the end of study (p>0.05 for all parameters, except for alveolar congestion (p=0.0401) (Figures 1 and 2).

DISCUSSION

One-lung ventilation is a routinely used mechanical ventilation technique in the practice of thoracic surgery. Although it has been recently become an indispensable technique for thoracic surgery, it may cause more lung damage, compared to TLV.[7] In surgical interventions performed with OLV, hypoxic pulmonary vasoconstriction induced by the collapse of the lung and reperfusion that takes place with reexpansion is responsible for reperfusion injury.[7] Additionally, ultrastructural and mechanical effects caused by surgical manipulation are associated with additional damage on the tissue. In surgical procedures performed with OLV, immediate adverse effects may be associated with the duration of OLV. In a study in rats by Tekinbas et al.,[22] lung damage increased along with prolonged duration of OLV. In another study, 212 patients were examined for reexpansion-reperfusion damage in a prospective manner and with

prolonged duration of OLV, the amount of superoxide radicals in the tissue were found to increase, indicating an increasing damage in the lung tissue.[23] In our study, 60 min of OLV, followed by 30 min of TLV were applied considering the mean duration of thoracic surgery operations via thoracotomy. In addition to well-documented antioxidant effects of melatonin, we investigated its protective effects on lung damage following OLV in rats. In our study, we obtained tissue samples after OLV and TLV and measured MDA, SOD, and TNF-α levels with histopathological examinations.

The MDA is the end-product of lipid peroxidation which is involved in oxidative damage and is one of the most important indicators of OLV-associated oxidative damage.[23] In our study, in the tissue samples of the rats receiving melatonin, MDA levels were found to be lower both at the end of OLV and TLV, compared to the control group. This finding suggests that melatonin reduces ischemia-reperfusion damage-associated lipid peroxidation in the lung tissue. In the literature, there are several studies that support this finding. In a study by Inci et al.,[24] single-lung transplantation was performed in rats and ischemia-reperfusion damage following transplantation was examined. In the study group, the rats received 10 mg/kg melatonin before the transplantation. In the melatonin group MDA levels were lower, compared to the control group, indicating the protective effects of melatonin on ischemia-reperfusion damage. Also, some other studies showed that when oxidative stress occurred not through ischemia-reperfusion, but via infection or thermal injury in the lung tissue, melatonin still decreased the levels of MDA and that it was tissue-protective.[25,26] All these findings are in consistent with our study results. Another finding is that MDA levels measured after OLV within the groups were lower than the levels measured after TLV both for melatonin and control groups. These findings do not correlate with the sequential damage anticipated due to reexpansion-reperfusion by transitioning to TLV. However, it is well-established that the blood flow in the lungs decreases by nearly 50% due to hypoxia during OLV.[6] Thus, the ischemic period occurring in the lung tissue during OLV is different than the classical ischemic period where the blood flow stops completely. During OLV, the blood flow continues, despite being reduced. In the light of these data, we can suggest that after the semi-ischemic period during 60 min of OLV, reperfusion damage may be less than that is observed after classical ischemia. This can explain why MDA levels measured after TLV did not increase, compared to post-OLV measurement.

The SOD is one of the enzymatic antioxidants found inside the cells and is one of the defense mechanisms against ischemia-reperfusion damage. It is a metalloenzyme catalyzing the dismutation of superoxide to hydrogen peroxide. In our study, in the tissue samples of the rats receiving melatonin, the mean SOD levels were measured to be higher both after OLV and TLV, compared to the control group. This finding indicates that melatonin activates the defense mechanisms against ischemia-reperfusion damage in the tissue. In the literature, there are several studies showing that melatonin increases SOD levels in the lung tissue against oxidative stress induced by different mechanisms, although not being via ischemia-reperfusion.[25,27] In a study by Huang et al.,[25] mouse lungs were infected with respiratory syncytial virus and SOD levels were found to decrease as a response to oxidative stress as expected, and the use of melatonin reversed this effect. In another study, the antioxidant effect of melatonin in the rats with phosgene-induced lung injury was investigated.[27] The melatonin group received melatonin at a dose of 10 mg/kg prior to exposure, and the mean SOD levels were measured in the lung tissue, which were significantly higher than the control group. In our study, the increase in the SOD levels in the melatonin group was more significant at the end of OLV. At the end of TLV, the mean SOD levels of the melatonin group were also higher than the control group, indicating the activating effects of melatonin on SOD. Considering intra-group analysis, at the end of TLV, both in melatonin and in control groups, the mean SOD levels were significantly lower than the levels at the end of OLV. This is thought to be associated with the consumption of SOD in the tissue. Furthermore, this decrease was correlated with the MDA levels at the end of both OLV and TLV.

One-lung ventilation and subsequent TLV do not only result in lipid peroxidation in the tissue. This process activates proinflammatory cytokines and contributes to lung damage. The TNF-α is a cytokine secreted from many cells from the body, but mainly from activated macrophages.[28] It is a polypeptide molecule and plays a role in inflammation and production of its signs. With the produced inflammatory effect, the blood flow in the tissue is blocked, thereby, leading to the most important effect of TNF-α which is tissue necrosis.[28] In an experimental study conducted by Leite et al.,[9] the effects of OLV on proinflammatory cytokines were examined. The rats were separated into two groups. The first group had one-hour OLV, followed by TLV. After one-hour TLV, bronchoalveolar lavage samples were obtained. The second group had three-hour OLV, followed by TLV. Bronchoalveolar lavage samples were

obtained after one-hour TLV. In the rats undergoing OLV, TNF-α levels were found to be higher than the controls and this increase was even more evident with prolonged duration of OLV.

Previous studies in the literature have shown that melatonin suppresses the inflammatory response in addition to its protective effects against oxidative damage and indirectly exerts its effects on TNF-α which is a proinflammatory cytokine. Gitto et al.[29] performed a study including 110 newborns with respiratory distress syndrome. Half of the patients received melatonin at a dose of 10 mg/kg for 10 times, while the other group received placebo. At the end of the study, TNF-α levels were measured in the tracheobronchial aspiration specimens. At 0 and 24 hours, TNF-α levels did not differ significantly between the groups. However, the TNF-α levels were found to significantly decrease in the patients receiving melatonin at 72 hours and on Day 7. In another study by Huang et al.,[25] the use of melatonin after lung damage caused by respiratory syncytial significantly decreased the TNF-α levels. Similarly, in our study, there was a significant decrease in the mean TNF-α levels measured both at the end of OLV and TLV compared to the control group. This finding suggests that melatonin has protective effects on tissue damage caused by inflammation in lungs where OLV was used, consistent with the existing data in the literature.

In control and melatonin groups, we evaluated tissue samples obtained at the end of OLV and TLV based on the presence and amount of alveolar congestion, leukocyte infiltration, and intra-alveolar bleeding. In consistent with the biochemical alterations, we might anticipate that OLV would also damage the lungs histopathologically and that melatonin would have protective effects against this damage, as well. In the OLV study conducted by Tekinbas et al.,[22] the rats had one-, two-, and three-hour OLV, followed by two-hour TLV. The control groups were ventilated with three-, four-, and five-hour TLV, respectively. At the end of the study, lung tissue samples were examined for alveolar edema, leukocyte infiltration, focal bleeding, and alveolar structure integrity. In groups having OLV for different durations, there was a significant histopathological damage, compared to the control group. This damage was even more significant in the rats having OLV for two and three hours. In another experimental study, Pedreira et al.[21] implemented two different ventilation strategies in mice as low- and high-pressure ventilation and examined out the effects of melatonin on lung damage after ventilation. At the end of the study, particularly in mice which were ventilated under high pressure, there was more lung damage and melatonin was found to reduce lung edema and tissue damage in these mice. In our study, we found that the amount of tissue alveolar congestion was significantly lower in the melatonin group, compared to the control group. The fact that melatonin significantly decreased alveolar congestion in the melatonin group, compared to the control group, at the end of the study showed that it exerted protective effects on rats ventilated with OLV. In addition, when the samples were evaluated for PMNL, lymphocyte infiltration, and intra-alveolar bleeding, melatonin decreased all these findings, despite not reaching a level of statistical significance.

Nonetheless, there are some limitations to the present study. Although melatonin showed a protective effect on lung injury after OLV, the effect of fractionated oxygen used in the ventilation of rats may have contributed the oxidative damage. Therefore, further studies including differently oxygenated rat groups are needed to clarify the issue.

In conclusion, our study results showed that melatonin decreased the levels of biochemical markers associated with oxidative stress and inflammation in the lung tissues of rats undergoing one-lung ventilation and reduced the findings of histopathological damage. Therefore, in complicated subjects and mainly in cancer patients undergoing OLV with prolonged duration of surgery who have high potential for oxidative-inflammatory tissue damage, the use of preoperative melatonin hypothetically can reduce postoperative lung damage.

Declaration of conflicting interests

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REFERENCES

1. Wolthuis EK, Vlaar AP, Choi G, Roelofs JJ, Juffermans NP, Schultz MJ. Mechanical ventilation using non-injurious ventilation settings causes lung injury in the absence of pre-existing lung injury in healthy mice. Crit Care 2009;13:R1.
2. Tobin MJ. Principles of mechanical ventilation. In: Fishman AP, Elias JA, Fishman JA, Grippi MA, Senior RM, Pack AI, editors. Fishman's Pulmonary Diseases and Disorders. New York: McGraw-Hill; 2008. p. 2675-89.
3. Gattinoni L, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. Crit Care Med 2010;38:S539-48.

4. Brodsky JB. The evolution of thoracic anesthesia. Thorac Surg Clin 2005;15:1-10.
5. Geze Ş, Tekinbaş C, Ulusoy H, Menteşe A, Topbaş M, Karaca M. One-lung ventilation duration-dependent stress response in thoracotomies and the effect of a low-volume, high-frequency differentiated ventilation strategy on this response. Turkish Journal of Thoracic and Cardiovascular Surgery 2019;27:336-42
6. Nakamura M, Fujishima S, Sawafuji M, Ishizaka A, Oguma T, Soejima K, et al. Importance of interleukin-8 in the development of reexpansion lung injury in rabbits. Am J Respir Crit Care Med 2000;161:1030-6.
7. Lohser J. Evidence-based management of one-lung ventilation. Anesthesiol Clin. 2008 ;26(2):241-72.
8. Cheng YD, Gao Y, Zhang H, Duan CJ, Zhang CF. Effects of OLV preconditioning and postconditioning on lung injury in thoracotomy. Asian J Surg 2014;37:80-5.
9. Leite CF, Calixto MC, Toro IF, Antunes E, Mussi RK. Characterization of pulmonary and systemic inflammatory responses produced by lung re-expansion after one-lung ventilation. J Cardiothorac Vasc Anesth 2012;26:427-32.
10. Wang J, Yi X, Jiang L, Dong H, Feng W, Wang S, et al. Protective effects of dexmedetomidine on lung in rats with one-lung ventilation. Exp Ther Med 2019;17:187-92.
11. Reiter RJ. Melatonin: the chemical expression of darkness. Mol Cell Endocrinol 1991;79:C153-8.
12. Erlich SS, Apuzzo ML. The pineal gland: anatomy, physiology, and clinical significance. J Neurosurg 1985;63:321-41.
13. Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernández-Montesinos R, Guerrero JM, et al. The modulatory role of melatonin on immune responsiveness. Curr Opin Investig Drugs 2006;7:423-31.
14. Arendt J. Melatonin. Clin Endocrinol (Oxf) 1988;29:205-29.
15. Kuş İ, Sarsılmaz M. Pineal Bezin Morfolojik Yapısı ve Fonksiyonları. T Klin J Med Sci 2002;22:221-6
16. Zang LY, Cosma G, Gardner H, Vallyathan V. Scavenging of reactive oxygen species by melatonin. Biochim Biophys Acta 1998;1425:469-77.
17. Longoni B, Salgo MG, Pryor WA, Marchiafava PL. Effects of melatonin on lipid peroxidation induced by oxygen radicals. Life Sci 1998;62:853-9.
18. Hardeland R, Balzer I, Poeggeler B, Fuhrberg B, Uría H, Behrmann G, et al. On the primary functions of melatonin in evolution: mediation of photoperiodic signals in a unicell, photooxidation, and scavenging of free radicals. J Pineal Res 1995;18:104-11.
19. Reiter RJ, Tan DX, Manchester LC, Qi W. Biochemical reactivity of melatonin with reactive oxygen and nitrogen species: a review of the evidence. Cell Biochem Biophys 2001;34:237-56.
20. Rodriguez C, Mayo JC, Sainz RM, Antolín I, Herrera F, Martín V, et al. Regulation of antioxidant enzymes: a significant role for melatonin. J Pineal Res 2004;36:1-9.
21. Pedreira PR, García-Prieto E, Parra D, Astudillo A, Diaz E, Taboada F, et al. Effects of melatonin in an experimental model of ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2008;295:L820-7.
22. Tekinbas C, Ulusoy H, Yulug E, Erol MM, Alver A, Yenilmez E, et al. One-lung ventilation: for how long? J Thorac Cardiovasc Surg 2007;134:405-10.
23. Misthos P, Katsaragakis S, Milingos N, Kakaris S, Sepsas E, Athanassiadi K, et al. Postresectional pulmonary oxidative stress in lung cancer patients. The role of one-lung ventilation. Eur J Cardiothorac Sur 2005;27:379-82.
24. Inci I, Inci D, Dutly A, Boehler A, Weder W. Melatonin attenuates posttransplant lung ischemia-reperfusion injury. Ann Thorac Surg 2002;73:220-5.
25. Huang SH, Cao XJ, Liu W, Shi XY, Wei W. Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. J Pineal Res 2010;48:109-16.
26. Sener G, Sehirli AO, Satiroğlu H, Keyer-Uysal M, Yeğen BC. Melatonin improves oxidative organ damage in a rat model of thermal injury. Burns 2002;28:419-25.
27. Zhang L, Shen J, Gan ZY, He DK, Zhong ZY. Protective effect of melatonin in rats with phosgene-induced lung injury. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2012;30:834-8.
28. Aggarwal B, Vilcek J (editors). Tumor Necrosis Factor: Structure, Function and Mechanism of Action. Marcel Dekker, 1992, pp 1-624
29. Gitto E, Reiter RJ, Sabatino G, Buonocore G, Romeo C, Gitto P, et al. Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: improvement with melatonin treatment. J Pineal Res 2005;39:287-93.