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The neuroprotective effect of melatonin in preventing vancomycin-induced neurotoxicity

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Abstract

Aim: Vancomycin is a commonly used antibiotic with potent activity against Gram-positive organisms, but prolonged use and high doses can lead to toxicity. While vancomycin-associated nephrotoxicity is widely reported, few cases of neurotoxicity have been described. Presupplementation with melatonin, a powerful antioxidant for nervous tissues, protects the sciatic nerve against all of the changes.

Materials and Methods: Melatonin, a neurosecretory product of the pineal gland, functions as an antioxidant in vivo and in vitro. Therefore, in this study the effect of melatonin in rats treated with vancomycin on the sciatic nerve was investigated. 28 wistar albino female rats were divided into four groups, each containing 7 rats. The first group was used as a control. The second group, melatonin (10 mg/kg/day) was injected intraperitoneally into rats for 7 days, respectively. The rats in the third group were injected with vancomycin (200 mg/kg) for 7 days, respectively. The fourth group, vancomycin (200 mg/kg)+melatonin (10 mg/kg/day) were received vancomycin for 7 days and than melatonin into rats for 7 days, respectively. The experiment was continued for 15 days. The sciatic nerve tissues were examined under light microscopes.

Results: According to our findings, S100 expression was lowest in the vancomycin-treated group. In addition, the immunoreactivity intensity of S100 was significantly increased in the vancomycin+melatonin group, compared to the vancomycin group ($p < 0.01$). However, the immunoreactivity intensity of UCHL in the vancomycin group was no statistically significantly than the immunoreactivity intensity of UCHL in the other groups ($p > 0.05$).

Conclusion: In this study, it was found that melatonin treatment effects positively regeneration of sciatic nerve injury caused by vancomycin in the sciatic nerve of rats.

Introduction

Vancomycin is a tricyclic glycopeptide antibiotic that was first isolated from the Streptococcus orientalis bacteria. Vancomycin is prescribed to treat and prevent gram-positive bacterial infections, such as methicillin-resistant Staphylococcus aureus (MRSA). Streptococci, enterococci, and methicillin-susceptible Staphylococcus aureus (MSSA) infections are also treated with it [1-3]. Common adverse effects of intravenous vancomycin injection encompass nephrotoxicity, hypotension, and allergic reactions. Additionally, among its side effects are allergic reactions, hypotension, Red man syndrome, phlebitis, neutropenia, thrombocytopenia, and local neurotoxic effects [4,5]. Patients being treated with oral vancomycin who have intestinal disease and poor renal function may take in and accumulate excessive serum levels of vancomycin, causing unusual neurological toxication symptoms such as headache, altered state of consciousness, confusion, and drowsiness in conjunction with sexual dysfunction [6]. When injected intraventricularly, vancomycin has been found to have local neurotoxic effects. Pleocytosis and eosinophilia have been seen in the cerebrospinal fluid (CSF), which is assumed to be the result of a vancomycin-induced inflammatory process in the CSF [7,8]. As a result, when used to treat ventriculitis, cancomycin has been linked to neurotoxic effects. After taking vancomycin intravenously for Enterococcus fecalis, Nava-Ocampo et al.[7] described a neonate who developed ventriculitis, CSF pleocytosis, and eosinophilia. This impact was considered to be mediated by a vancomycin-induced inflammatory process in the CSF.When given intravenously, the dose of vancomycin should be reduced to 5 mg/day [9]. Vancomycin is widely used in intensive care units, and it is

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necessary to improve the knowledge of neurotoxic effects and the safe use of vancomycin.

Melatonin is produced by the pineal gland, which is located at the base of the brain (N-acetyl-5-methoxytryptamine). Melatonin has a variety of roles in the human body, including circadian rhythms, sleep physiology, mental status, reproduction, tumor growth, aging, and a variety of other physiologic processes. Its many functions in the human body are still unknown [10]. Furthermore, early melatonin administration following traumatic sciatic nerve injury caused by acute injury may reduce lipid peroxidation, axonal damage, and myelin destruction [11].

Melatonin's effects on probable vancomycin harm in the peripheral nervous system have been studied in a few research, but the effects of vancomycin and melatonin on the sciatic nerve are inadequately researched in the literature. In this respect, our study will make important contributions to the literature. This study aims to investigate the protective effects of melatonin supplementation on acute vancomycin-induced changes in the sciatic nerve.

Materials and Methods

Experimental design and animal groups

All animal treatments were approved by Erciyes University's Experimental Animal Ethical Committee (Decision number: 22/082). The investigation was carried out in compliance with the Animal Experiments Local Ethics Committee's guidelines for the care and use of laboratory animals (Faculty of Medicine, Erciyes University, and Animal Health Institute, Turkey). A total of 28 healthy female Wistar albino rats were used in this study. Rats were housed in ventilated plastic cages with a 12/12 h light/dark cycle and free access to normal rat food and tap water at a regulated temperature (22°C). The rats were fasted for around 24 hours before the experiment, and only water was given to them. The experimental rats were divided into four groups, each with seven animals (control, melatonin (10 mg/kg/day), vancomycin (200 mg/kg), and vancomycin+melatonin) [12]. The control group was given a conventional diet and water. In the melatonin group, the rats were given 10 mg/kg/day of melatonin intraperitoneally (i.p.) once a day for seven days. The vancomycin-treated group received 200 mg/kg i.p. twice a day with a 12-hour gap in the vancomycin group for seven days. The rats in the treatment group received 200 mg/kg vancomycin twice daily with a 12-hour interval for seven days, followed by melatonin (10 mg/kg/day) once daily for seven days in the vancomycin+melatonin group. Melatonin treatment (10 mg/kg/day) began on day eight and was continued until day seven. At the end of the experiment, the rats were decapitated under light ether anesthesia.

Histopathological analysis

Sciatic nerve tissue sections from the research groups were fixed in 4% paraformaldehyde for histological investigation. Cryosections of 6–8 µm were produced from cryomatrix-embedded tissues. The preparations were stained with Oil red O to reveal the myelin sheath after normal follow-up. Images were acquired using a DP71 digital camera (Olympus Corp., Tokyo, Japan) mounted to a BX51 light microscope after the staining technique (Olympus Corp., Tokyo, Japan). Edema, axonal degeneration, and myelin degradation were all considered during the histological examination. In the study, microscopic photographs were taken randomly from 10 different areas at x100 magnification to show the differences between the axon diameter and axon number of the experimental groups. Myelinated nerve fibers were counted and recorded in each group using the Image J software program (ImageJ, National Institute of Health, USA). In addition, the diameters of 1000 axons from the experimental group were calculated using Image J software again, and statistical analysis of the obtained data was performed [13,14].

S100 and UCHL immunofluorescence staining

Cryosections (7 µm) were air-dried for 10 minutes, then fixed in acetone at 20°C for 10 minutes before being air-dried again at room temperature. The slides were preincubated with normal goat serum (10% in tris-buffered saline) for 20 minutes after being rinsed three times in TBS for five minutes each time. S-100 (Anti-S100; Invitrogen, Waltham, MA, USA) or UCHL were applied to the sections directly, and the slides were incubated overnight at 4°C in a humidity chamber. The sections were stained with goat anti-mouse secondary antibody and conjugated with rhodamine-labelled goat anti-mouse antibody (1:200 dilution in PBS; Jackson ImmunoResearch, Newmarket, UK) for 45 minutes after washing three times in TBS for 5 minutes each time. The slides were cleaned three times in TBS for five minutes each time. The cryosections were counterstained with DAPI (Sigma, St. Louis, USA) for 1 minute after steps. Fluoromount-G was used to mount the slides (Southern Biotechnologies, Birmingham, USA). Primary antibodies were not used as a negative control in immunostaining tests.

The immunostaining intensity levels for the identified antigens were compared using Image J software and quantitative immunohistochemistry (ImageJ, National Institute of Health, USA). Each rat's S100 and UCHL immunostaining intensities were randomly set for 5 separate visual fields and assessed. Using Image J software and high power fields (400 magnification), the mean immunostaining intensities for S100 and UCHL were computed.

Statistical analysis

The mean and standard deviation of all data were calculated using GraphPad Prism 8 (Graphpad Prism 8.00, Graphpad Software, USA). One-way ANOVA was used to establish statistical significance. The Kolmogorov-Smirnov test was utilized to see if the data was regularly distributed. Statistical significance was defined as p 0.05.

Results

Light microscopic evaluation

A histomorphological examination of the sciatic nerve of rats was undertaken to determine the recovery impact of melatonin in vancomycin-induced damage. Axons, myelinated and unmyelinated fibers, and Schwann cells all displayed normal characteristics in slides stained with Oil red O. Melatonin and control rats (Figure 1). Vancomycin,

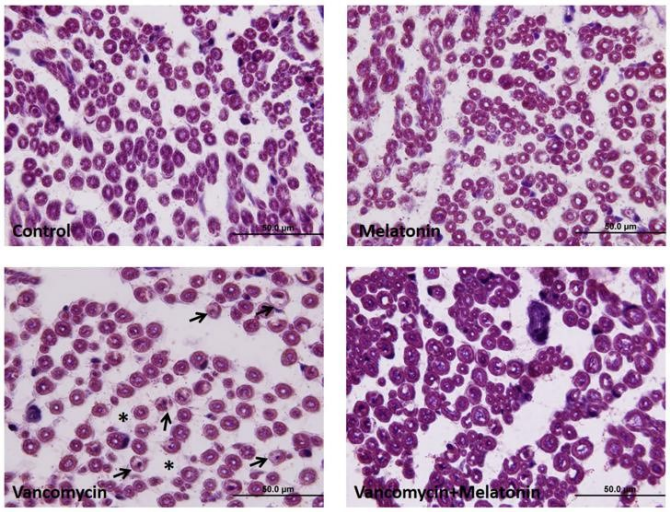

Figure 1. A micrograph demonstrating fine features of a sciatic nerve of a rat from control and melatonin group. The oil red O staining was used to evaluate myelination. Myelinated and unmyelinated fibers shows normal features. The axons appears unremarkable and demonstrates no morphologic abnormality. The nucleus of schwann cells with normal are also seen. A micrograph from a rat sciatic nerve after Vancomycin treatment. There are edema (*) axonal degeneration. (arrow). A picture showing a section from the sciatic nerve from a rat which was treated with melatonin before vancomysin treatment. Damage on the axons decreased remarkably (Oil Red O staining, 100x).

on the other hand, produced axonal injury in the majority of myelinated axons. Swollen axons and axonal injury were prevalent and some unmyelinated fibers had vacuolization and degeneration in this group. The tissues of rats treated with melatonin revealed fewer morphologic changes when examined histologically. Melatonin administration resulted in a considerable reduction in myelin breakdown. The characteristics of axons improved dramatically in vancomycin+melatonin group.

When the axon diameters of all groups were compared statistically ($p<0.001$), the lowest axon diameter belongs to the control and melatonin groups, the highest axon diameter belongs to the vancomycin group (Figure 1). This result suggests that it is caused by the edema caused by vancomycin in nerve fibers.

Furthermore, there were no significant variations in axon number per visual field between the control and vancomycin groups. According to our findings, the axon number in the vancomycin group was similar to that in the control group. As demonstrated in Figure 1, the number of axons per visual field did not differ statistically significantly between the control and experimental groups ($p > 0.05$).

Immunofluorescence findings

S100 and UCHL immunofluorescence staining were chosen for this section of the study, and expression intensities in the sciatic nerve areas of these antibodies were calculated. When the S100 immunoreactivity intensities in the sciatic nerve were compared to other groups, the sciatic nerve sections from the vancomycin group had the lowest expression. Interestingly, when S100 expression in the vancomycin+melatonin group was evaluated, the S100 immunoreactivity intensity showed almost as much as the control group (Figure 2, Figure 4). In this study, the vancomycin+melatonin group had a statistically significant increase in S100 immunoreactivity in the sciatic nerve as compared to the vancomycin group ($p < 0.01$).

Moreover, when the UCHL immunoreactivity intensity was compared between the experimental groups; UCHL values differed statistically in the experimental groups ($p<0.05$). The highest UCHL value belonged to the control and melatonin groups, while the lowest UCHL value belonged to the vancomycin group. Interestingly, the immunoreactivity intensity of UCHL in the vancomycin+melatonin group treated with melatonin was similar to the control group (Figure 3, Figure 4).

Discussion

Antibiotic-related adverse effects are common in hospitalized patients. Antibiotics' ability to control infection and create a favorable therapeutic outcome for patients is being harmed by the widespread proliferation of multi-resistant and pan-resistant bacteria that have acquired multiple multi-resistance mechanisms [15]. In this study, we examined how melatonin affected a vancomycin-treated rat sciatic nerve and discussed the putative cytoprotective mechanisms of melatonin against vancomycin-induced sciatic nerve. The primary purpose of this study was to investigate if melatonin could protect peripheral nerves from vancomycin harm. The theory was tested in the rat sciatic nerve using histopathological and immunofluorescent findings.

Vancomycin is a glycopeptide antibiotic used to treat acute bacterial infections caused by microorganisms that are resistant to other antibiotics, as well as patients who are allergic to penicillin and cephalosporin products. It is also used empirically in critically ill patients to treat organisms like methicillin-resistant Staphylococcus aureus [16].

Furthermore, vancomycin is still a viable option for treating bacterial endocarditis in penicillin-allergic patients and those with gram-positive penicillin-resistant infections. It has been linked to side effects while being proven to be safe at therapeutic serum concentrations. Antibiotic dosage is critical for effective treatment and the prevention of antibiotic resistance [17]. Vancomycin is a time-dependent killing antibiotic that works best when the concentration at the infection site stays above the minimum inhibitory concentration for the duration of the dosage interval. Chest pain, hypotension, and muscle spasms are all possible side effects. Furthermore, ototoxicity, neutropenia, fixed drug eruptions, fever, phlebitis, nephrotoxicity [18,19], thrombocytopenia [19], and pancytopenia [20] are some of the other side effects. Despite the lack of impaired renal function and known risk factors for systemic

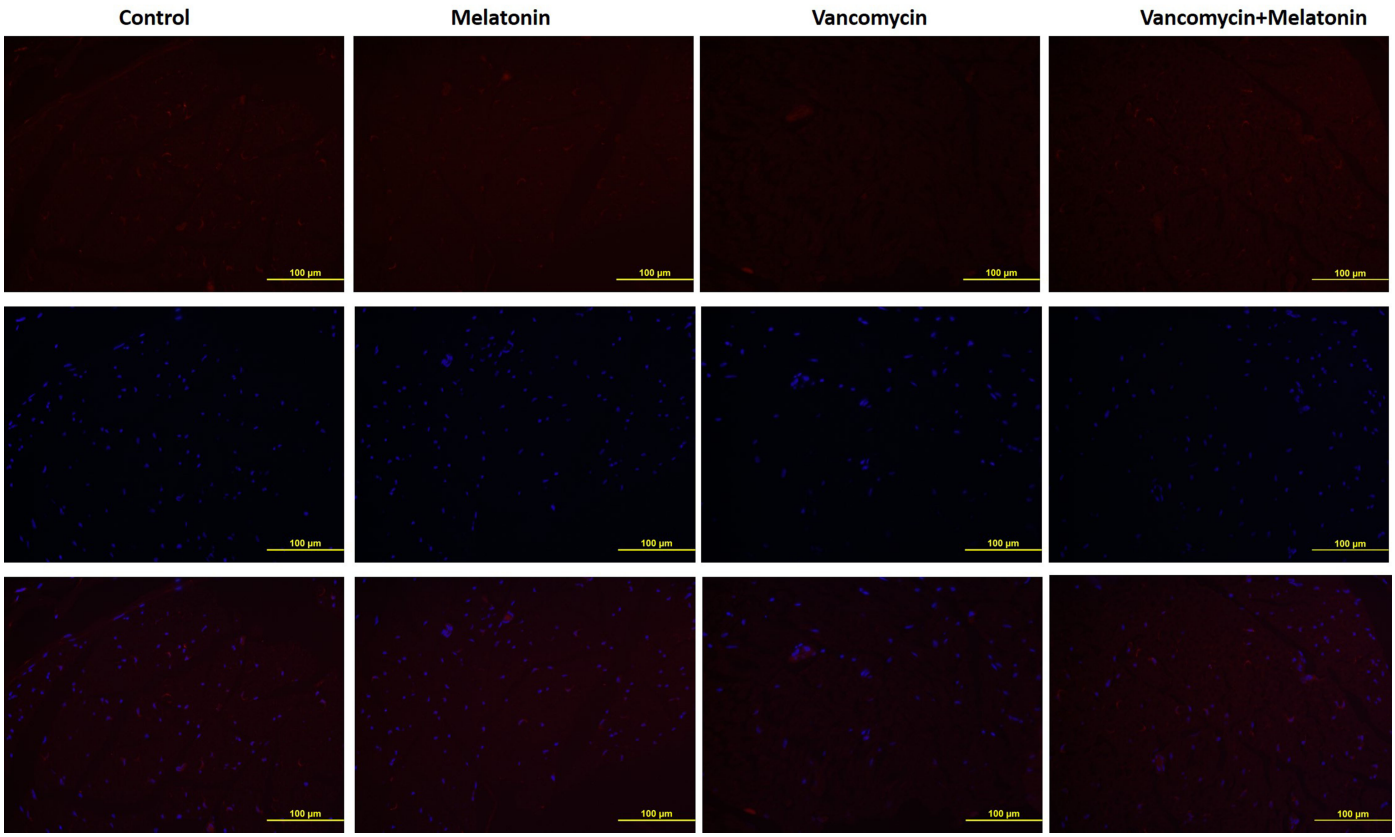

Figure 2. Representative photomicrographs of S100 immunostaining of nerve fiber sections in the experimental groups (S100 immunofluoresan staining, 40x).

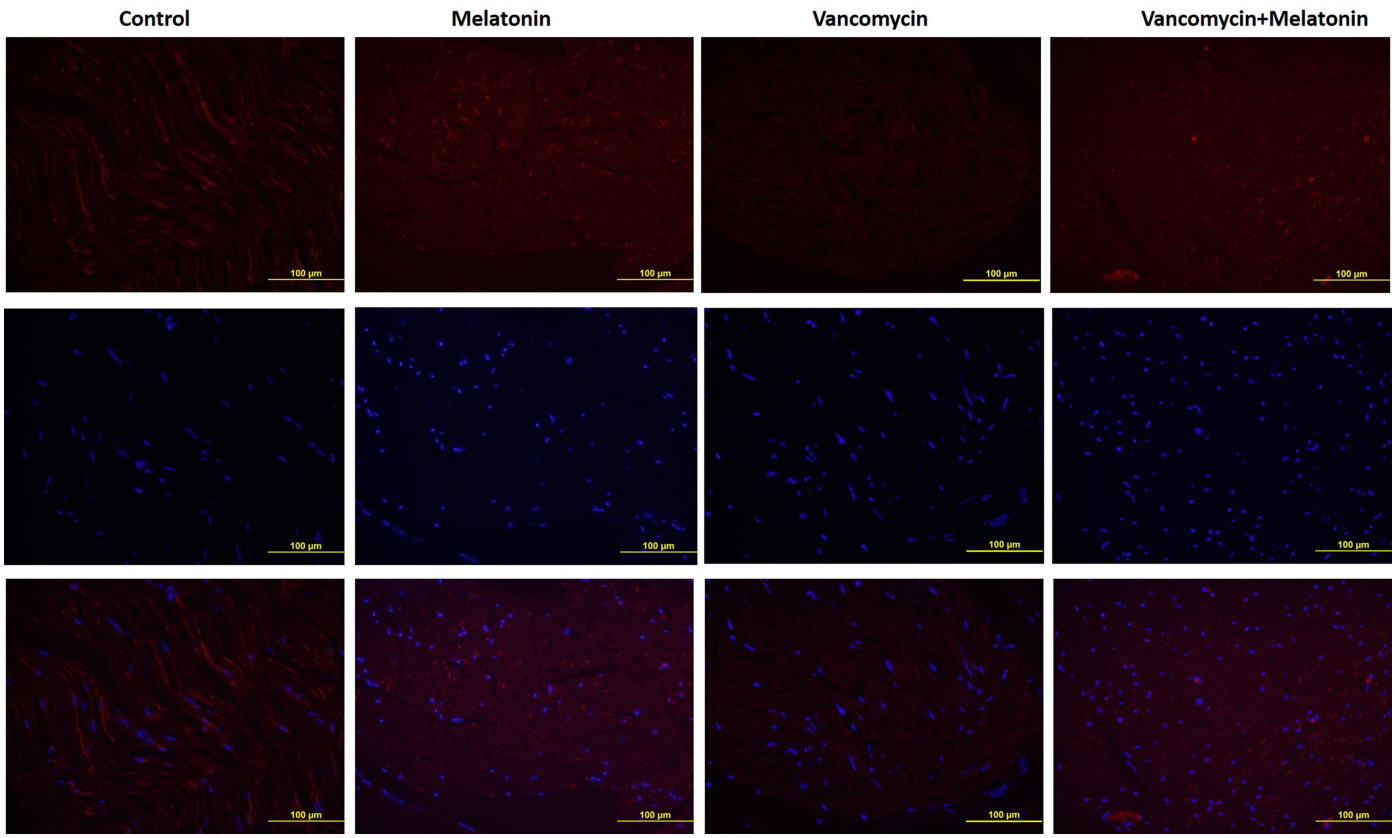

Figure 3. Representative photomicrographs of UCHL immunostaining of nerve fiber sections in the experimental groups (UCHL immunofluoresan staining, 40x).

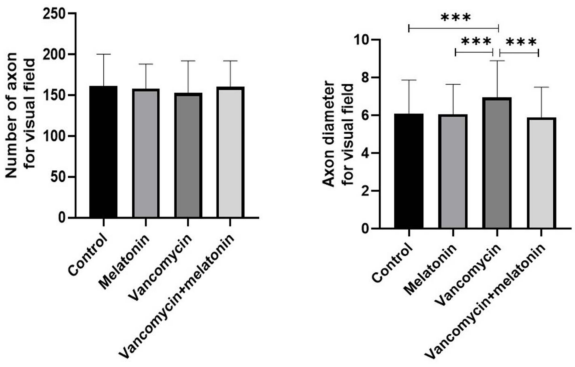

Figure 4. Effects of melatonin on S100 and UCHL immunoreactivity intensities against vancomycin-induced nerve damage compared to vancomycin administered rats. p<.05; **p<.01; **p<.001.

exposure to vancomycin, a case of vancomycin toxicity was unusual; the patient presented with symptoms indicating neurotoxicity that may promote or resemble mild encephalitis. The patient was not taking any other medications that could cause neurotoxicity or have potential pharmacological interactions with vancomycin. About 24 hours after quitting the medicine, a test of vancomycin serum level of 2.2 mcg/dL confirmed systemic absorption [6]. According to the authors, the case was termed a "likely" drug response due to an oral vancomycin adverse reaction [21].

This study found that even in the absence of renal impairment or other established risk factors for systemic absorption, vancomycin might eventually reach hazardous levels. In this study, we showed that vancomycin causes axonal damage such as, edema, axonal degeneration and myelin damage. When the histological findings in this study were evaluated using a light microscope, the histological appearance of sciatic nerve architecture from the vancomycin+melatonin group was close to that of the control group. Additionally, analysis of histomorphometric findings of axon diameter revealed that they were similar between the groups (control, melatonin and vancomycin+melatonin) and statistically significantly lower than those seen in the vancomycin group. In terms of the quantity of axons per visual field, however, there was no significant difference between the groups.

Melatonin (N-acetyl-5-methoxy tryptamine) is one of the oldest compounds that can be traced back to the origin of life and is a regularly used medicine in the treatment of nerve injury. The pineal gland, as well as extra-pineal sources such as the gut and skin, the retina, the testes, the ovary, the placenta, glial cells, and lymphocytes, release this neurohormone. It has a high lipophilicity, allowing it to pass through cellular and physiological barriers. Melatonin is prevalent in all organisms and interacts with reactive oxygen species (ROS) produced during respiration to produce 3-hydroxymelatonin and other metabolites that are greater radical scavengers than melatonin [22,23].

Melatonin has several functions as a powerful free radical scavenger, including neuroprotection, antioxidant, anti-inflammatory immunomodulation, and protection of macromolecules (such as DNA) from oxidative damage [24]. Moreover, it is known to have a favorable effect on myelin content and axon quantity by reducing collagen, inhibiting neuroma and scar tissue formation at nerve injury sites, and encouraging Schwann cell proliferation [25]. Melatonin differs from other hormones in that it has both receptor-independent and receptor-dependent actions. Melatonin's hormonal effects can be seen in the control of reproductive activity, sleep improvement, immune response enhancement, carcinogenesis suppression, stem cell synthesis elevation, anti-inflammatory action, and the protection of many age-related disorders [23]. Since S100 is a schwann cell marker in peripheral nerve tissue and S100-negativity in damaged nerves is a finding of nerve damage, S100-positivity is regarded as a positive marker of nerve regeneration (26). The S-100 protein level is known to decrease in the event of nerve damage and can be illustrated using immunohistochemical staining [26,27]. In terms of the general immunohistochemical analysis findings in this study, S100 immunoreactivity intensity revealed similar expression in the the control and vancomycin+melatonin groups. Because it regulates protein activity, the ubiquitin system is essential for practically all cellular functions. Ubiquitin C-terminal hydrolase ligase (UCHL, also known as protein gene product (PGP9.5)) has recently been shown to play a suppressive role in inflammation [28], in addition to its critical role in proteasomal degradation [29].

It has been frequently employed as a marker for peripheral nerve fibers due to its abundance in UCHL nerves. UCHL is required for maintaining axonal integrity. UCHL is a frequently used marker for innervation and structures containing neuropeptides [30]. According to our findings, vancomycin-induced injury to the sciatic nerve does not rule out UCHL downregulation.

Conclusion

The main finding of this study is that pretreatment with vancomycin damages the sciatic nerve. Furthermore, post-melatonin treatment resulted in fewer morphologic changes in the peripheric nerve characteristics. When prescribing vancomycin therapy, the possibility of systemic absorption and probable vancomycin neurotoxicity should be considered. Additionally, the lowest S100 and UCHL immunoreactivity intensity value was obtained in the vancomycin group in this study. In terms of the general immunoreactivity intensity analysis findings in this study, the S100 and UCHL immunoreactivity intensity revealed similar expression in the control, melatonin, and vancomycin+melatonin groups. Combined analysis of the histological and light microscopy findings showed that melatonin treatment, suggesting that it may be suitable alternative therapy.

Ethics approval

All animal treatments were approved by Erciyes University's Experimental Animal Ethical Committee (Decision number: 22/082). The investigation was carried out in compliance with the Animal Experiments Local Ethics

Committee's guidelines for the care and use of laboratory animals (Faculty of Medicine, Erciyes University, and Animal Health Institute, Turkey).

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