DOI: 10.4149/BLL_2023_010

Bratisl Med J 2023; 124 (1)

64 – 69

EXPERIMENTAL STUDY

Demonstration of the protective effect of propofol in rat model of cisplatin-induced neuropathy

Edip GONULLU[1], Gozde DAGISTAN[2], Yuksel ERKIN[3], Mumin Alper ERDOGAN[4], Oytun ERBAS[5]

Izmir Katip Celebi University, Faculty of Medicine, Department of Physiology, Izmir, Turkey.
alpero86@gmail.com

ABSTRACT
Cisplatin is commonly used in the treatment of lung, genitourinary, and gastrointestinal cancers. Peripheral neuropathy is the most important side effect, leading to a decrease in the dose of cisplatin or its complete cessation in the early period. 16 rats were given cisplatin at a dose of 2.5 mg/ kg/day twice a week for 4 weeks to induce neuropathy model. The rats taking Cisplatin were divided into 2 groups. Group 1 rats (n = 8) were given 1 ml/kg/day 0.9 % NaCl intraperitoneally, and Group 2 rats were given 10 mg/kg/day Propofol intraperitoneally daily for 4 weeks. The remaining 8 rats served as the control group. At the end of the study, all animals were tested for motor functions. Blood samples were collected for the measurement of plasma lipid peroxidation (malondialdehyde; MDA), tumor necrosis factor (TNF-α), glutathione (GSH), IL-6 and HSP-70 levels. Electromyography findings revealed that compound muscle action potential (CMAP) amplitude was significantly higher in the cisplatin-Propofol group than in the cisplatin-saline group. Also, cisplatin-Propofol treated group showed significantly lower TNF-α, MDA and IL-6 levels and higher GSH and HSP-70 levels than cispalatin-Saline group ($p < 0.01$, $p < 0.001$). In addition, while the CMAP latency was decreased in the propofol group, the CMAP amplitude was increased, and a significant improvement was observed in the Inclined test scores. Besides, histological examinations showed an increase in axon diameter and NGF expression with Propofol treatment. This study demonstrated that Propofol exerts protective activity against cisplatin-induced neurotoxicity by increasing endogenous antioxidants and reducing lipid peroxidation and inflammation *(Tab. 3, Fig. 4, Ref. 30)*. Text in PDF *www.elis.sk*
KEY WORDS: cisplatin, neuropathy, propofol, oxidative damage, ınflammation.

Introduction

Cisplatin-induced peripheral neuropathy (CIPN) is a common dose-limiting side effect in patients receiving chemotherapy, and one of the most important mechanisms playing a role in its pathogenesis is oxidative stress (2). The oxidant/antioxidant mechanism kept in balance with antioxidant activity under normal conditions is sometimes impaired at the expense of antioxidant activity (4, 5). Cisplatin exerts its pro-oxidant effect by increasing lipid peroxidation and inducing the formation of free oxygen radicals. Excessive production of reactive oxygen species (ROS) plays a role in the pathogenesis by damaging cell components and impairing their functions (3).

As a result of a decreased neural transmission rate, peripheral neuropathy is characterized by the loss of vibration and position senses and the tingling, dysesthesia and the loss of tendon reflexes (4–6). Electrophysiological and histological studies have shown that cisplatin has detrimental effects on both human and animal nervous systems (5, 7–9). Cisplatin-induced cytotoxicity is caused by oxidative stress, DNA damage, and inflammatory cytokines [10]. When it comes to neurotoxicity, the pathophysiological mechanisms that contribute to this include inflammation and oxidative damage as well as DNA damage and apoptotic cell death in the nervous system (11, 12).

The creation of reactive oxygen causes lipid peroxidation, which results in the formation of malondialdehyde (MDA). One of the most well-known functions of glutathione (GSH) is its ability to regulate the immune system and reduce the effects of oxidative stress. When it comes to oxidative stress, cytokines such as tumor necrosis factor-alpha (TNF-) and interleukin IL-6 are critical (6–8).

Hsp70 proteins, which reduce apoptosis, are the basic components of the protein translocation systems of the endoplasmic reticulum (ER) and mitochondria (24). Besides, extracellular HSP70s have a number of cytoprotective and immunomodulatory features (25).

[1]Anesthesiology and Reanimation Department (Algology), İzmir Bakircay University, Faculty of Medicine, Izmir, Turkey, [2]Anesthesiology and Reanimation Department (Algology), Akdeniz University, Faculty of Medicine, Antalya, Turkey, [3]Anesthesiology and Reanimation Department (Algology), Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey, [4]Izmir Katip Çelebi University, Faculty of Medicine, Department of Physiology, Izmir, Turkey, and [5]Demiroglu Bilim University, Faculty of Medicine, Department of Physiology, Istanbul, Turkey

Address for correspondence: Mumin Alper ERDOGAN, Assoc Prof, DVM, PhD, Izmir Katip Celebi University, Faculty of Medicine, Department of Physiology, Izmir, Turkey.
Phone: +905433818677

The discovery of the physiological effects of neurotrophin nerve growth factor (NGF) on the autonomic nervous system, sensory system, central nervous system, immunological and endocrine system dates back to the 1950s. Its trophic effect on neurons in the peripheral nervous system is important in maintaining the functional integrity of cholinergic neurons in the central nervous system as well as maintaining the functions of the immune system. From this aspect, it is reported to be useful in Alzheimer's and peripheral neuropathies (26).

Propofol is a fast-acting anesthetic agent administered intravenously. In addition to its anesthetic effects, it has been reported in previous studies that it protects cells and tissues from oxidative stress, reduces apoptosis and inflammation, and protects against hypoxic/ischemic-induced neuronal damage (9–13). In a study conducted on rats with traumatic brain injury in the literature, the neuroprotective and anti-inflammatory effects of propofol were emphasized (14). Propofol has lipid peroxidation inhibitory effects as well as reactive oxygen species scavenging effects. This feature of propofol is associated with phenolic hydroxyl group similar to alpha-tocopherol with natural antioxidant properties in its structure (3).

Based on this information, we evaluated the therapeutic effects of propofol in CIPN in rats with electromyography (EMG) recordings and sciatic nerve biochemical analysis (HSP 70 protein) and immunohistochemical method (NGF expression, axon diameter). We also examined the effect of propofol on MDA, GSH, IL-6, and TNF-α levels, which are important markers for lipid peroxidation and antioxidative capacity.

Materials and methods

Animals

24 adult female Wistar rats, weighing 200–210 g, were used in the study. Animals were housed in cages and maintained under standard conditions with 12-hour light/dark cycles at room temperature (22 ± 2 °C). Throughout the research, they were provided a regular pellet diet and water a la carte. The University of Science University's Institutional Animal Care and Ethical Committee accepted the study's procedure (Ethical Number: 20210621). Unless otherwise stated, all compounds were purchased from Sigma-Aldrich Inc.

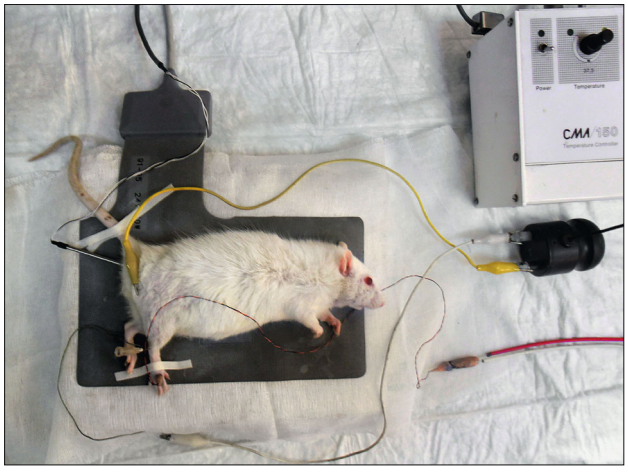

Fig. 1. EMG recording system.

Fig. 2. Inclined plane test system.

Experimental procedure

24 rats were included in the study. Eight rats were included in the study as a normal control group. No, the drug was given for this group.

Cisplatin was given to 16 rats twice a week for four weeks at a dose of 2.5 mg/kg/day (a total of 20 mg/kg) to produce neuropathy. Two sets of Cisplatin-treated rats were created. Saline and propofol were administered intravenously to eight rats in each group for four weeks. Group 1 rats were given 1 ml per kg per day of 0.9 percent NaCl, and Group 2 rats received 10 milligrams per kilogram of body weight of propofol (Propofol, Abbott, 10 mg/mL) per day. Cisplatin and Saline-treated rats perished during the research. There was no death in rats receiving cisplatin and propofol.

At the end of the study, all animals were tested for motor function and EMG. Then, the rats were sacrificed under high-dose anesthesia by applying a cervical dislocation procedure. Blood was drawn for biochemistry.

Measurement of lipid peroxidation (MDA)

Malondialdehyde (MDA) levels as thiobarbituric acid reactive compounds were used to detect lipid peroxidation in plasma samples (TBARS). Trichloroacetic acid and TBARS reagent were added to plasma samples, mixed, and incubated for 60 minutes at 100 °C. The samples were centrifuged at 3000 rpm for 20 minutes after cooling on ice, and the absorbance of the supernatant was measured at 535 nm. MDA levels were measured in nanograms and calibrated with tetraethoxypropane.

Measurement of tissue glutathione (GSH) levels

The amount of GSH in plasma samples was determined spectrophotometrically using Ellman's technique. Thiols react with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to produce a colored anion with a maximum peak at 412 nm in this technique. The stan-

dard calibration curve was used to calculate GSH levels, which were given as M.

Measurement of plasma TNF- α, IL-6 levels

Plasma TNF-α, IL-6 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Biosciences).

Sciatic nerve biochemical analysis

Sciatic nerves were quickly extracted after decapitation and kept at 20 °C until biochemical assays were done. Whole nerve tissues were homogenized in 5 volumes of phosphate-buffered saline (PBS) five times the volume of the acquired tissue (pH 7.4) and centrifuged at 5,000 g for 15 minutes for tissue analysis. Total protein concentration in innerve homogenates was evaluated using Bradford's technique and bovine serum albumin as a reference. Using commercially available rat ELISA kits, the levels of HSP-70 in the tissue supernatants were evaluated in the sciatic nerves.

Electrophysiological recordings

Recordings of electrophysiology EMG investigations were conducted 10 days following cisplatin administration. The right sciatic nerve was stimulated supramaximally (intensity 10 V, duration 0.05 ms, frequency 1 Hz, in the range of 0.5–5000 Hz, 40 kHz/s with a sampling rate) three times using a bipolar subcutaneous needle stimulation electrode (BIOPAC Systems, Inc, Santa Barbara, CA). Unipolar platinum electrodes were used to record CMAPs from 2-3 interosseous muscles (Fig. 1). Biopac Student Lab Pro version 3.6.7 software (BIOPAC Systems, Inc) was used to analyze the data, with distal latency and CMAP amplitude as the parameters. During the EMG recordings, the rats' rectal temperatures were measured using a rectal probe (HP Viridia 24-C; Hewlett-Packard Company, Palo Alto, CA), and the temperature of each rat was regulated between 36 and 37 degrees Celsius using a heating pad. Animals were euthanized after EMG recordings, and blood samples were taken by heart puncture for biochemical analysis. They were centrifuged for 10 minutes at 3000 rpm at room temperature before being stored at –20 °C until the assay.

Assessment of motor function

The rats' motor abilities were assessed using the Rivlin and Tator approach, which included an inclined-plate test. The rat was put on an inclined plate with its long axis oblique to the rat's body. The inclined plate's initial angle was 10 degrees. The inclination angle gradually increased, and the motor score was calculated as the greatest angle of the plate on which the rat maintained its position for 5 seconds without dropping. Each rat's inclined plate angle was measured three times to get an average result (Fig. 2).

Histology and quantitative immunohistochemistry

Rats were perfused intracardially with 4 % formaldehyde for histology and quantitative immunohistochemistry. Briefly, sciatic nerves were embedded in paraffin, sectioned at 5 µm thickness via microtome (Leica RM 2145). All sections were photographed with Olympus C-5050 digital camera mounted on an Olympus BX51 microscope. Axonal thickness was measured using Image-Pro Express 1.4.5 (Media Cybernetics, Inc. USA).

Sections were treated with 10 % H_2O_2 for 30 minutes to remove endogenous peroxidase activity before being blocked with 10 % normal goat serum (Invitrogen) for 1 hour at room temperature for immunohistochemical analysis. After that, slices were treated for 24 hours at 4 °C with primary antibodies against nerve growth factor (NGF) (Santacruz Biotechnology; 1/100). The Histostain-Plus Bulk kit (Invitrogen) was used to detect antibodies against rabbit IgG, and 3,3' diaminobenzidine (DAB) was utilized to view the final product. All sections were cleaned in PBS before being inspected with an Olympus BX51 microscope and photographed with an Olympus C-5050 digital camera. Quantitative immunohistochemistry was performed on all groups and six slices from each animal. Under a light microscope at x100 magnification, two blinded observers counted the total immune-positive Schwann cells. Data were expressed as mean ± SEM.

Statistical analysis

SPSS version 15.0 for Windows was used to conduct the statistical analysis. The Student's t-test and analysis of variance were used to compare the groups of parametric variables. The Mann–Whitney U test was also used to compare the groups of non-parametric variables. In addition, the Shapiro–Wilk test was employed to differentiate between parametric and non-parametric data. The results are given as mean+SEM. Statistical significance was defined as a $p < 0.05$. A $p < 0.05$ was accepted as statistically significant.

Results

Plasma malondialdehyde, glutathione, tumor necrosis factor-α and IL-6 levels

MDA, TNF-α, IL-6 levels were significantly higher in the cisplatin-saline group compared to the control group ($p < 0.0001$, $p < 0.01$, $p < 0.0001$, respectively). In the cisplatin-propofol group, these values were significantly lower than those in the cisplatin-saline group (IL-6: $p < 0.0001$, TNF-α and MDA: $p < 0.001$) (Tab. 1).

GSH was significantly lower in the cisplatin-saline group compared to the control group ($p < 0.01$). In the cisplatin-propofol

Tab. 1. The effects of propofol on plasma TNF-α, MDA, IL-6, GSH levels in all groups.

	Control	Cisplatin + Saline	Cisplatin + 10 mg/kg propofol
MDA (nM)	57.1±6.4	142.6±16.4 **	89.5±7.3 #
TNF-alfa (pg/ml)	20.8±1.1	84.2±5.5 *	44.3±1.9 #
IL-6 (pg/ml)	10.7±0.4	745.1±32.9 **	284.6±13.5 ##
GSH (µM)	13.5±1.2	5.1±1.8 *	11.7±2.4 #
Sciatic nerve HSP-70 (mcg/mg protein)	7.2±0.8	9.1±2.3	24.1±3.8 ##

Results are presented as mean ± SEM. Statistical analyses were performed by one-way ANOVA test. *$p < 0.01$, **$p < 0.0001$ (different from control group), #$p < 0.001$, ##$p < 0.0001$ (different from cisplatin and saline group)

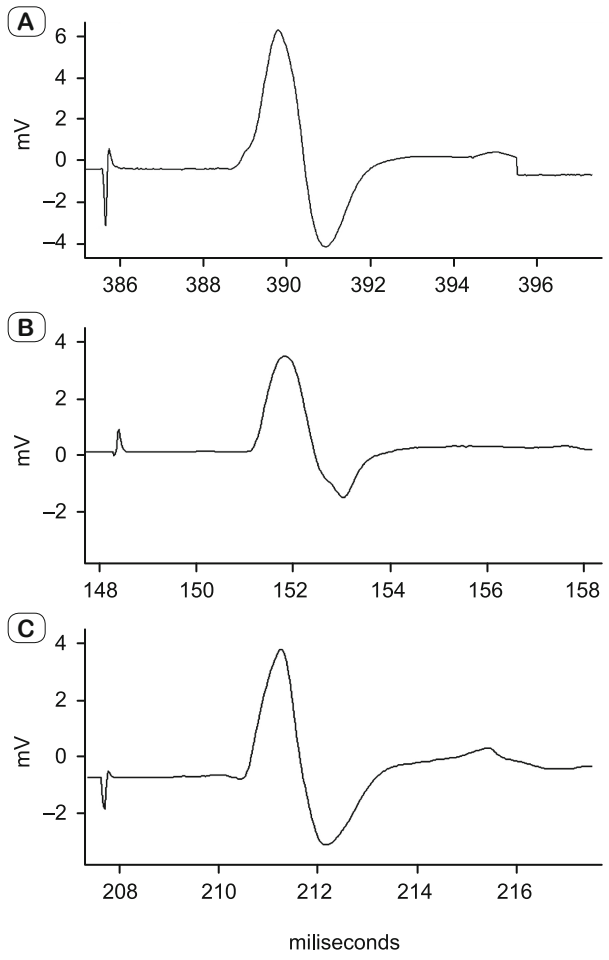

Fig. 3. EMG record. A) Normal Group, B) Cisplatin + Saline Group, C) Cisplatin + propofol Group.

group, GSH level was significantly higher than in the cisplatin-saline group ($p < 0.001$) (Tab. 1).

HSP-70 protein from sciatic nerve biochemical analysis was also significantly higher in the cisplatin-propofol group compared to the cisplatin-saline group ($p < 0.0001$) (Tab. 1).

Electrophysiology analysis

Figure 3 shows the alterations in EMG recordings in all groups. In this study, CMAP amplitude was found to be significantly lower in the cisplatin-saline group compared to the control group ($p < 0.01$). CMAP amplitude was found to be significantly higher in the cisplatin-propofol group compared to the cisplatin-saline group ($p < 0.05$) (Tab. 2).

CMAP latency was significantly higher in the cisplatin-saline group compared to the control group ($p < 0.05$). However, in the cisplatin-propofol group, CMAP latency was significantly higher compared to the cisplatin-saline group ($p < 0.05$) (Tab. 2).

While the inclined plane score was significantly lower in the cisplatin-saline group compared to the control group ($p < 0.01$), it was significantly higher in the cisplatin-propofol group compared to the cisplatin-saline group ($p < 0.001$) (Tab. 2).

Immunohistochemical examination of sciatic nerve tissue samples

While NGF expression was significantly lower in the cisplatin-saline group compared to the control group ($p < 0.01$), it was significantly higher in the cisplatin-propofol group compared to the cisplatin-saline group ($p < 0.001$). While axon diameter was significantly lower in the cisplatin-saline group compared to the control group, it was significantly higher in the cisplatin-propofol group compared to the cisplatin-saline group ($p < 0.05$) (Tab. 3, Fig. 4).

Discussion

In this study, we demonstrated the beneficial effects of propofol in CIPN in rats, both in EMG recordings and immunohistochemistry. Besides, we demonstrated the positive effects of propofol on antioxidant/oxidant balance with MDA, GSH, TNF-α, IL-6 levels. In various previous studies conducted, it has been shown that propofol prevents apoptosis, has anti-inflammatory and antioxidant effects and has taken its place in the literature (9–18). Based on this feature on propofol, we investigated whether it has a curative effect on neurotoxicity by developing a peripheral neurotoxicity model in rats. To the best of our knowledge, our study is the first study in which EMG and immunohistochemical evaluation with antioxidant/oxidant levels to evaluate the results of propofol ad-

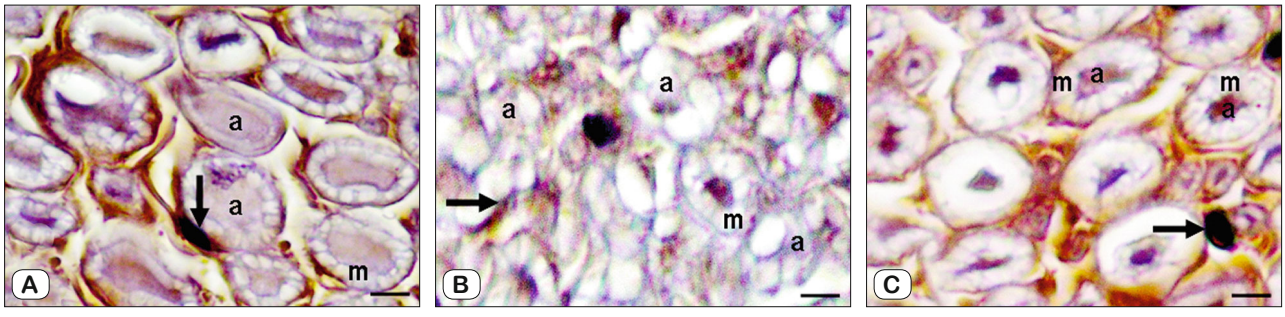

Fig. 4. NGF immunohistochemistry. a-b-c: x 100 magnification, A) Normal Group, (a): axon, arrow: Schwann cell, (m): myelin sheat, B) Cisplatin + Saline Group, decreased axon diameter and NGF expression, degenerated myelin sheat C) Cisplatin + propofol Group, increased axon diameter and NGF expression, improved myelin sheat.

Tab. 2. The effects of Propofol on CMAP latency, CMAP amplitude inclined plane score in all groups.

	Control	Cisplatin + Saline	Cisplatin + 10 mg/kg propofol
CMAP latency (ms)	2.12±0.03	2.65±0.08 *	2.48±0.05 #
CMAP amplitude (mV)	13.3±0.2	4.8±0.2 **	7.6±0.4 #
Inclined plane score (°)	98.6±7.5	78.5±6.2 **	95.4±4.9 ##

Results are presented as mean ± SEM. Statistical analyses were performed by one-way ANOVA test. *p < 0.05, ** p < 0.01 (different from control group), # p < 0.05, ## p < 0.001 (different from cisplatin and saline group)

Tab. 3. The effects of propofol on plasma NGF expression and axon diameter in all groups.

	Control	Cisplatin + Saline	Cisplatin + 10 mg/kg propofol
NGF expression (%)	82.7±6.8	29.4±9.3 **	65.1±5.6 ##
Axon diameter, μm	3.32±0.25	2.1±0.18 *	2.84±0.31 #

Results are presented as mean ± SEM. Statistical analyses were performed by one-way ANOVA test. *p < 0.05, ** p < 0.01 (different from control group), # p < 0.05, ## p < 0.001 (different from cisplatin and saline group)

ministration in CIPN was used. Previous clinical and experimental studies conducted have shown that antioxidant agents can prevent cisplatin-induced neurotoxicity (19, 20).

Zhou and Qiu experimentally demonstrated that the subanesthetic dose of propofol improved cisplatin-related cognitive functions. They reported that this improvement occurred by preventing neuronal apoptosis (21). Moghadam et al reported that propofol has an antioxidant effect in cisplatin-induced nephrotoxicity, suppresses apoptosis, and supports mitochondrial activity (3). Roh GU et al. reported that IL-6, the most important marker of the inflammatory response to tissue damage in patients undergoing radical prostatectomy, decreased with propofol administration, which was related to the anti-inflammatory feature of propofol.

However, no significant change in TNF-α was recorded in the same study (22). Numerous antioxidants, including flavonoids, vitamin E, and vitamin C, are known to work as free radical scavengers (3). In our study, the beneficial effects of propofol on oxidant-antioxidant balance, EMG recordings, and immunohistochemical evaluation were revealed. These positive effects may be related to the fact that the content of propofol is a phenolic hydroxyl group similar to vitamin E. Unlike Moghadam (3) studies, EMG recordings and immunohistochemical properties of the subjects were examined, and a significant healing effect of propofol on NGF and axon diameter was observed in our study. Akman et al. demonstrated the positive effects of oxytocin in CIPN using EMG recordings. In their study, they found that the CMAP amplitude was significantly higher in rats given cisplatin-oxytocin compared to the group that received cisplatin-saline. They found that CMAP latency was shortened in the treated group, but this shortening was not statistically significant (6). In our study, similar to Akman's study, we found that CMAP amplitude increased significantly after propofol in rats with CIPN and that the CMAP latency was shortened, but this shortening was statistically insignificant. In addition, an inclined plane score was recorded in EMG in our study. We found this value to be significantly lower in the group receiving Cisplatin-Saline compared to the control group, and this value to be statistically higher in the cisplatin-Propofol-treated group compared to the CIPN-treated group.

Zhang et al showed the beneficial effects of HSP 70, which contains constitutive and excitatory proteins, in demyelinating neuropathies in rodents (23, 27). Ma et al (28) reported that impaired neuronal mitochondrial bioenergetics leads to the pathophysiological progression of diabetic neuropathy and that KU-32 treatment increases the level of HSP 70 and contributes to mitochondrial recovery. They also reported that the cytotoxicity antagonizing effect of HSP 70 could be a guide in the treatment of other neurodegenerative diseases (28). In our study, we detected increased HSP 70 protein level in the sciatic nerve biochemical analysis in the group receiving cisplatin-propofol, and this was further evidence of the benefit of propofol in CIPN.

In our study, it was shown that NGF expression, known to be a good marker of peripheral nerve regeneration and axon diameter were evaluated, and both were significantly increased in the propofol-treated group compared to the CIPN-treated group.

In the literature, it has been reported that the fibrin adhesive membrane containing NGF is very useful for nerve regeneration in peripheral nerve injuries (29). Similar to our findings regarding NGF and axon diameter, Gürkan et al (30) published that in their experimental sciatic nerve injury models, the gallic acid they applied in addition to the surgical treatment increased the expression percentage of NGF and the number of axons. They showed that gallic acid has positive effects on peripheral nerve damage recovery due to its anti-inflammatory and antioxidant effects (30).

Conclusion

Our findings showed that propofol attenuated oxidative damage in cisplatin-induced neurotoxicity and played a curative role in EMG and histopathology. Findings obtained from our study suggest that propofol is promising for patients suffering from CIPN.

References

1. Zhou J, Fan Y, Zhong J, Huang Z, Huang T, Lin S, Chen H. TAK1 mediates excessive autophagy via p38 and ERK in cisplatin-induced acute kidney injury. J Cell Mol Med 2018; 22 (5): 2908–2921.

2. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst 2019; 24 (Suppl 2): S26–S39.

3. Taheri Moghadam G, Hosseini-Zijoud SM, Heidary Shayesteh T, Ghasemi H, Ranjbar A. Attenuation of cisplatin-induced toxic oxidative stress by propofol. Anesth Pain Med 2014; 4 (4): e14221.

4. Lorente L, Martín MM, Abreu-González P, Ramos L, Cáceres JJ, Argueso M, Solé-Violán J, Jiménez A, García-Marín V. Maintained high sustained serum malondialdehyde levels after severe brain trauma injury in non-survivor patients. BMC Res Notes 2019; 12 (1): 789.

5. Soni H, Kaminski D, Gangaraju R, Adebiyi A. Cisplatin-induced oxidative stress stimulates renal Fas ligand shedding. Ren Fail 2018; 40 (1): 314–322

6. Akman T, Akman L, Erbas O, Terek MC, Taskiran D, Ozsaran A. The preventive effect of oxytocin to Cisplatin-induced neurotoxicity: an experimental rat model. Biomed Res Int 2015; 2015: 167235.

7. So H, Kim H, Lee JH et al. Cisplatin cytotoxicity of auditory cells requires secretions of proinflammatory cytokines via activation of ERK and NF-κB. J Assoc Res Otolaryngol 2007; 8 (3): 338–355.

8. Minich DM, Brown BI. A Review of Dietary (Phyto)Nutrients for Glutathione Support. Nutrients 2019; 11 (9): 2073.

9. Yao W, Luo G, Zhu G, Chi X, Zhang A, Xia Z et al. Propofol activation of the Nrf2 pathway is associated with amelioration of acute lung injury in a rat liver transplantation model. Oxid Med Cell Longev 2014; 258567 doi: 10.1155/2014/258567

10. Lee S, Kim K, Kim YH, Chung MH, Kang I, Ha J et al. Preventive role of propofol in hypoxia/reoxygenation-induced apoptotic H9c2 rat cardiac myoblast cell death. Mol Med Rep 2011; 4: 351–356.

11. Ji C, Yi H, Huang J, Zhang W, Zheng M. Propofol alleviates inflammation and apoptosis in HCY-induced HUVECs by inhibiting endoplasmic reticulum stress. Mol Med Rep 2021; 23 (5): 333.

12. Wu GJ, Chen WF, Hung HC, Jean YH, Sung CS, Chakraborty C, Lee HP, Chen NF, Wen ZH. Effects of propofol on proliferation and anti-apoptosis of neuroblastoma SH-SY5Y cell line: new insights into neuroprotection. Brain Res 2011; 1384: 42–50.

13. Zhang DX, Ding HZ, Jiang S, Zeng YM, Tang QF. An in vitro study of the neuroprotective effect of propofol on hypoxic hippocampal slice. Brain Inj 2014; 28: 1758–1765.

14. Cui C, Zhang D, Sun K, Li H, Xu L, Lin G, ... Sun Y. Propofol maintains Th17/Treg cell balance and reduces inflammation in rats with traumatic brain injury via the miR-145-3p/NFATc2/NF-κB axis. Internat J Mol Med 2021; 48 (1): 1–9.

15. Huang Y, Lei L, Liu Y. Propofol Improves Sensitivity of Lung Cancer Cells to Cisplatin and Its Mechanism. Med Sci Monit 2020; 26: e919786. DOI: 10.12659/MSM.919786. PMID: 32225124; PMCID: PMC7142322.

16. Liu Z, Zhang J, Hong G et al. Propofol inhibits growth and invasion of pancreatic cancer cells through regulation of the miR-21/Slug signaling pathway. Am J Transl Res 2016; 8: 4120–4133.

17. Zhang F, Wang C, Cui Y et al. Effects of propofol on several membrane characteristics of cervical cancer cell lines. Cell Physiol Biochem 2016; 40: 172–182.

18. Liu WZ, Liu N. Propofol inhibits lung cancer A549 cell growth and epithelial-mesenchymal transition process by upregulation of microRNA-1284. Oncol Res 2018; 27: 1–8.

19. Rezvanfar MA, Rezvanfar MA, Shahverdi RA et al. Protection of cisplatin-induced spermatotoxicity, DNA damage and chromatin abnormality by selenium nano-particles. Toxicol Appl Pharmacol 2013; 266: 356–365.

20. Tan DX, Manchester LC, Terron MP et al. One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res 2007; 42: 28–42.

21. Zhou Y, Qiu Y. Propofol alleviates cisplatin-related cognitive impairment. Neurol Sci 2019; 40 (8): 1645–1649.

22. Roh GU, Song Y, Park J, Ki YM, Han DW. Effects of propofol on the inflammatory response during robot-assisted laparoscopic radical prostatectomy: a prospective randomized controlled study. Sci Reports 2019; 9 (1): 1–9.

23. Baker TG, Roy S, Brandon CS, Kramarenko IK, Francis SP, Taleb M, Marshall KM, Schwendener R, Lee FS, Cunningham LL. Heat shock protein-mediated protection against Cisplatin-induced hair cell death. J Assoc Res Otolaryngol 2015; 16 (1): 67–80.

24. Chatterjee S, Burns TF. Targeting Heat Shock Proteins in Cancer: A Promising Therapeutic Approach. Int J Mol Sci 2017; 18 (9): 1978.

25. Radons J. The human HSP70 family of chaperones: where do we stand? Cell Stress Chaperones 2016; 21 (3): 379–404. DOİ: 10.1007/s12192-016-0676-6.

26. Aloe L, Rocco ML, Bianchi P, Manni L. Nerve growth factor: from the early discoveries to the potential clinical use. J Transl Med 2012; 10: 239.

27. Zhang X, Li C, Fowler SC, Zhang Z, Blagg BSJ, Dobrowsky RT. Targeting Heat Shock Protein 70 to Ameliorate c-Jun Expression and Improve Demyelinating Neuropathy. ACS Chem Neurosci 2018; 9 (2): 381–390.

28. Ma J, Farmer KL, Pan P, Urban MJ, Zhao H, Blagg BS, Dobrowsky RT. Heat shock protein 70 is necessary to improve mitochondrial bioenergetics and reverse diabetic sensory neuropathy following KU-32 therapy. J Pharmacol Exp Ther 2014; 348 (2): 281–292.

29. Ma S, Peng C, Wu S, Wu D, Gao C. Sciatic nerve regeneration using a nerve growth factor-containing fibrin glue membrane. Neural Regen Res 2013; 8 (36): 3416–3422.

30. Gurkan G, Erdogan MA, Yigitturk G, Erbas O. The Restorative Effect of Gallic Acid on the Experimental Sciatic Nerve Damage Model. J Korean Neurosurg Soc 2021; 64 (6): 873–881.

Received July 29, 2022.
Accepted August 24, 2022.