Investigation of the Neuro-Regenerative Effects of Bioresonance and Magnetotherapy in Sciatic Nerve Damage-Induced Rats

Investigación de los Efectos Neurorregenerativos de Biorresonancia y Magnetoterapia en Ratas Inducidas por Daño del Nervio Ciático

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SUMMARY: Peripheral nerve damage is a significant clinical problem that can lead to severe complications in patients. Regarding the regeneration of peripheral nerves, it is crucial to use experimental animals' nerves and use different evaluation methods. Epineural or perineural suturing is the gold standard in treating sciatic nerve injury, but nerve repair is often unsuccessful. This study aimed to investigate the neuroregenerative effects of magnetotherapy and bioresonance in experimental animals with sciatic nerve damage. In this study, 24 female Wistar rats were divided into 7 groups (n=6) as follows: Group 1 (Control), Group 2 (Axonotmesis control), Group 3 (Anastomosis control), Group 4 (Axonotmesis + magnetotherapy), Group 5 (Anastomosis + magnetotherapy), Group 6 (Axonotmesis + bioresonance), Group 7 (Anastomosis + bioresonance). Magnetotherapy and bioresonance treatments were applied for 12 weeks. Behavioural tests and EMG tests were performed at the end of the 12th week. Then the rats were sacrificed, and a histopathological evaluation was made. The statistical significance level was taken as 5 % in the calculations, and the SPSS (IBM SPSS for Windows, ver.21) statistical package program was used for the calculations. Statistically significant results were obtained in animal behaviour tests, EMG, and pathology groups treated with magnetotherapy. There was no statistically significant difference in the groups treated with bioresonance treatment compared to the control groups. Muscle activity and nerve repair occurred in experimental animals with acute peripheral nerve damage due to 12 weeks of magnetotherapy, and further studies should support these results.

KEY WORDS: Bioresonance; EMG; Magnetotheraphy; Nerve regeneration; Sciatic nerve.

INTRODUCTION

The sciatic nerve is the longest in the human body with the largest cross-sectional area. Trauma is the most common cause of sciatic nerve injuries. As a result of these damages, the sciatic nerve is either severed or severely damaged. Peripheral nerve injury is still a worldwide clinical problem that seriously affects patients' quality of life and causes economic burden in large populations. Damaged peripheral nerves can heal on their own, albeit to a certain extent. This situation varies from patient to patient. Of course, this situation is directly related to the extent and degree of peripheral nerve damage. However, for severe peripheral nerve damage, the regenerative abilities are very

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limited and the regenerative effects are very weak. It is obvious that there is a need for studies on an experimental basis to better understand the process following peripheral nerve injury (Qian *et al*., 2018). Fang *et al*. (2020) suggested that autologous nerve grafting is the most ideal strategy for the treatment of sciatic nerve injury. At the same time, they argued that this method sacrifices healthy nerves and is difficult to surgery, and that there may be a need for other advanced alternatives for nerve grafting. In addition, while these injuries create inconvenience for patients, they also make an enormous financial burden on society. According to a statistic from the United States, the annual cost of peripheral nerve damage treatment is $150 billion.

Current treatment approaches for peripheral nerve regeneration are self-healing, physiotherapy, and surgery. Generally, drug treatments aim to increase the patient's comfort and relieve their pain. The gold standard treatment method is nerve autologous nerve grafting (Sinis *et al*., 2005, 2011; Fang *et al*., 2020). In a review study, it was noted that many researchers are dealing with rodent peripheral nerves. It has been suggested that a popular animal model in the overall assessment is the rat median nerve model. It has also been stated that it has attracted the attention of many scientists in this field with its easy-going, simple behavioral tests and reliable long-term results (Sinis *et al*., 2011). In an experimental study, they demonstrated the important role of Schwann cells in the regeneration process in a 2 cm defect in the rat median nerve. Furthermore, as demonstrated in simple behavioral test, Schwann cell-filled nerve channels clearly induced functional recovery 9 months after implantation that was comparable to that of the autologous graft (Sinis *et al*., 2005). Even if it is accepted as gold standart treatment method, the low success rate of surgery and tissue rejection fail. Due to the limitations of all treatments, it is essential to develop new treatment approaches such as different physiotherapy methods, pulsed electromagnetic fields, and bioresonance for sciatic nerve regeneration. The roles played by these treatments in the healing processes are shown in the literature (Wilson & Jagadeesh, 1976; Ito & Bassett, 1983; Canè *et al*., 1993; Assiotis *et al*., 2012). Canè *et al*. (1993) concluded in an experimental study that pulsed low-frequency electromagnetic fields of low frequency not only stimulate bone repair, but also improve the osteogenic phase of the healing process. On the other hand, Assiotis *et al*. (2012) suggested that pulsed electromagnetic field stimulation is an effective, non-invasive method for addressing non-infected tibial union abnormalities. They concluded that its success was not associated with specific fracture or patient-related variables and could not be considered a clearly time-dependent phenomenon. A similar controlled study on spinal cord regeneration following hemichordotomy was initiated in an experimental study, and preliminary results showed that pulsed electromagnetic therapy induced nerve fiber regeneration along the scar site when animals were sacrificed three months after hemichordotomy (Wilson & Jagadeesh, 1976). With a similar technique, in the light of histological and functional data, pulsed electromagnetic fields have been reported to improve the speed and quality of peripheral nerve regeneration in the severed rat sciatic nerve approximately twofold (Ito & Bassett, 1983).

In this experimental study, the effectiveness of magnetotherapy and bioresonance treatments on nerve regeneration was investigated in experimental animals with sciatic nerve damage.

MATERIAL AND METHOD

Animals. Female Albino-Wistar rats (Gathered from Animal Experiments Local Ethics Committee of YÜHADYEK). Before the experiment, the animals were acclimated to laboratory conditions. All sciatic nerve behavioural tests were performed by a blinded investigator between 9:00 am and 5:00 pm.

Ethical permission. Experiment protocols were carried out with ethical permission from YÜHADYEK. It was performed in accordance with the 4R rule for minimal experimental animal use and welfare.

Experimental design. General anesthesia with xylazine/ ketamine was administered before each surgical procedure. A total of 42 female Albino-Wistar rats with an average weight of 250-300 g were used. Seven groups were formed, with six rats in each cage. The laboratory environment secured a room temperature of 20° Celsius with a relative humidity of 55 % and a night-day rhythm of 12 hours each.

Experimental groups:

Group 1: Control
Group 2: Anastomosis + Control
Group 3: Crushing + Control
Group 4: Anastomosis + Magnetotherapy
Group 5: Anastomosis + Bioresonance
Group 6: Crushing + Magnetotherapy
Group 7: Crushing + Bioresonance

Treatment

Magnetotheraphy. For 12 weeks, 20 magnetic magnets with

a strength of 0.02 tesla were placed evenly around the outer perimeter of the experimental animals' cages, resulting in a magnetic field of 0.4 tesla. During the experiment, the locations of the magnets were checked every day.

Bioresonance. The Biomedis trinity (China) device was charged daily, and a frequency of 0.00087 hertz was spread. The device was placed where the rats were gathered in the cage so that the experimental animals were exposed to the frequency equally for 12 weeks. The device was controlled throughout the experiment.

Functional behaviour test

Hot Plate Test. Hot-plate responses of rats are mainly used for combined results of peripheral and central mechanisms. In the hot-plate test, rats were housed one at a time on a hot plate set to a heated plate temperature of 52 ± 0.2 °C. The first sign of the rats' latency response was considered an indicator of the pain threshold with a claw pulling and/or jumping movements. The cutting time was accepted as 20 seconds to prevent damage to the rats' claws (Khalilzadeh *et al.*, 2018).

Rotarod test. Muscle activity will be measured on the rotarod instrument (Ugo Basile, Biological Research Apparatus, Varese, Italy) to detect rats' motor performance and coordination (Nehru *et al.*, 2008). The animals taken into the experiment will be acclimated to the rotarod device for three consecutive days. During this time, rats will be trained to walk on a rotating bar at a constant speed of 12 rpm for 2 mins. On the day of the test, 30 min before the experiments start, the animals will be taken to the laboratory to adapt to the environment. After the animals are taken to their chambers on the Rotarod device and are placed in the opposite direction of the rotating rod (7.3 cm in diameter), accelerating smoothly between 4 and 40 rpm over 5 minutes, their residence time on the rod will be automatically recorded. The recording time was determined as 300 s, and three consecutive measurements were made by applying 5-minute rest periods; and after each trial, the device will be wiped dry with 70 % ethanol solution (Assaf & Schiller, 2019).

EMG test. Motor nerve conduction velocity examination is a golden method for evaluating motor axon regeneration, myelination, and muscle innervation (Freeman Jr. *et al.*, 2003).

Motor nerve conduction velocity (MSH) is used to determine the speed at which the warning signal generated in the nerve fibers is transmitted to the distal nerves and muscles over the axons (Stanley, 1981).

Compound muscle action potential (CMAP) is determined by the nerve fiber's number of muscle fibers innervated. The number of motor units is evaluated by measuring the electrical potential of contraction in the muscle mass (Machida *et al.*, 1989).

Latency is evaluated as the period from the stimulation (stimulation) to the nerve fiber to the onset of deflection (the point at which the response begins and the electrical potential leaves the zero line) (English *et al.*, 2007).

Histopathological assesment. Samples were fixed in 10 % formaldehyde solution, embedded in paraffin, and 3-4 m sections were obtained. H&E (Hematoxylin-Eosin) and Toluidine Blue staining were done. An OlympusBX53 (Tokyo, Japan) light microscope evaluated the samples. Sections were evaluated regarding axonal degeneration, axonolysis (vacuolization), endoneurial edema, cellularity, foreign body reaction, and inflammation (Fig. 3).

It was evaluated as a percentage (%) and scored according to the degree of damage. No damage (0), light damage (1) (1-25 %), moderate damage (2) (25-75 %), severe damage (3) (75-100 %) (Table I). For statistical analysis, the nerve damage was scored at 10 percent intervals (Humphreys *et al.*, 1996). (0-100 %) All evaluations were made by a pathologist.

Statistical analysis. Descriptive statistics for the studied variables (traits) were presented as median, mean, standard deviation, minimum and maximum values. Kruskal-Wallis test was performed to compare groups. In addition, Wilcoxon test also used to compare side (left-right). Statistical significance level was considered as 5 % and SPSS (ver: 21) statistical program was used for all statistical computations.

RESULTS

Rotarod findings. According to the results of the rotarod formation, a statistically significant difference was found when the magnetotherapy+crushing applied group was compared with the healthy control and crushing control groups. No statistically significant difference was found when the bioresonance+crushing group was compared with the healthy control and crushing control groups. Significant differences were found when the magnetotherapy + anastomosis group was compared with the healthy control and anastomosis control groups. No significant difference was found when the bioresonance+anastomosis group was compared with the healthy control and anastomosis control groups (Fig. 1).
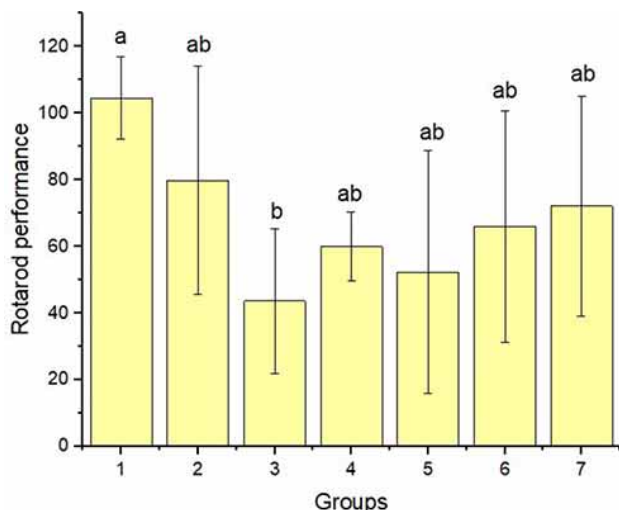
Fig. 1. Rotarod analysis results. a,b: Shows difference between groups.

Hot plate test findings. The hot plate test results showed a statistically significant difference when the magnetotherapy+crushing group was compared with the healthy control and crushing control groups. No statistically significant difference was found when the bioresonance+crushing group was compared with the healthy control and crushing control groups. Significant differences were found when the magnetotherapy+anastomosis group was compared with the healthy control and anastomosis control groups. No significant difference was found when the bioresonance+anastomosis group was compared with the healthy control and anastomosis control groups (Fig. 2).
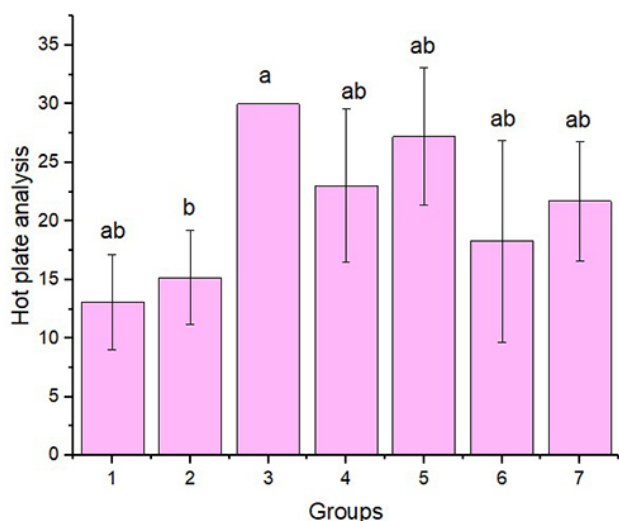

Fig. 2. Hot plate analysis results. (1=Control, 2=Anastomosis+control, 3=Crushing+control, 4=Anastomosis + magnetotherapy, 5=Anastomosis+bioresonance, 6=Crushing+ magnetotheraphy, 7=Crushing+bioresonance). a,b: Shows difference between groups.

EMG findings. Electrophysiological tests were performed at the end of the experimental study. Compound muscle action potential (CMAP) data were expressed in millivolts (mV), latency time in milliseconds (ms), and motor nerve conduction velocity (MSH) data in meters/second (m/s).

Latency: It was statistically significantly faster in the Group 3 and Group 1 groups than in the other groups (p =0.001). There was no significant difference between Group 1, Group 3, and Group 6 groups. There was no significant difference between Group 7, Group 5, Group 4, Group 6, and Group 2 groups.

Duration: It lasted statistically significantly longer in the Group 7 and Group 2 groups than in the other groups (p =0.0013). However, no significant difference was found between the Group 7 and Group 2 groups. In addition, no significant difference was found between the Group 5, Group 4, Group 3, Group 6, and Group 1 groups.

Compound muscle action potential (CMAP) amplitude: It was statistically significantly higher in the Group 3 group than in the other groups (p =0.002). There was no significant difference between Group 7, Group 5, Group 4, Group 3, Group 6, and Group 2 groups. There was no statistically significant difference between the groups.

Motor nerve conduction velocity (MNCV): It was statistically significantly faster in the Group 3 group than in the Group 5, Group 4, Group 6, and Group 2 groups (p =0.009). The conduction rate of the Group 3 group was significantly higher than the Group 5, Group 4, and Group 2 groups. There was no significant difference between Group 7, Group 5, Group 4, Group 6, and Group 2 groups. In addition, there was no significant difference between the Group 7, Group 3, and Group 1 groups.

Histopathological evaluation. (Fig. 3, Table I)

Table I. Comparison of percentage and severity of sciatic nerve injury between groups. No damage (0), light damage (1) (1-25 %), moderate damage (2) (25-75 %), severe damage (3) (75-100 %).

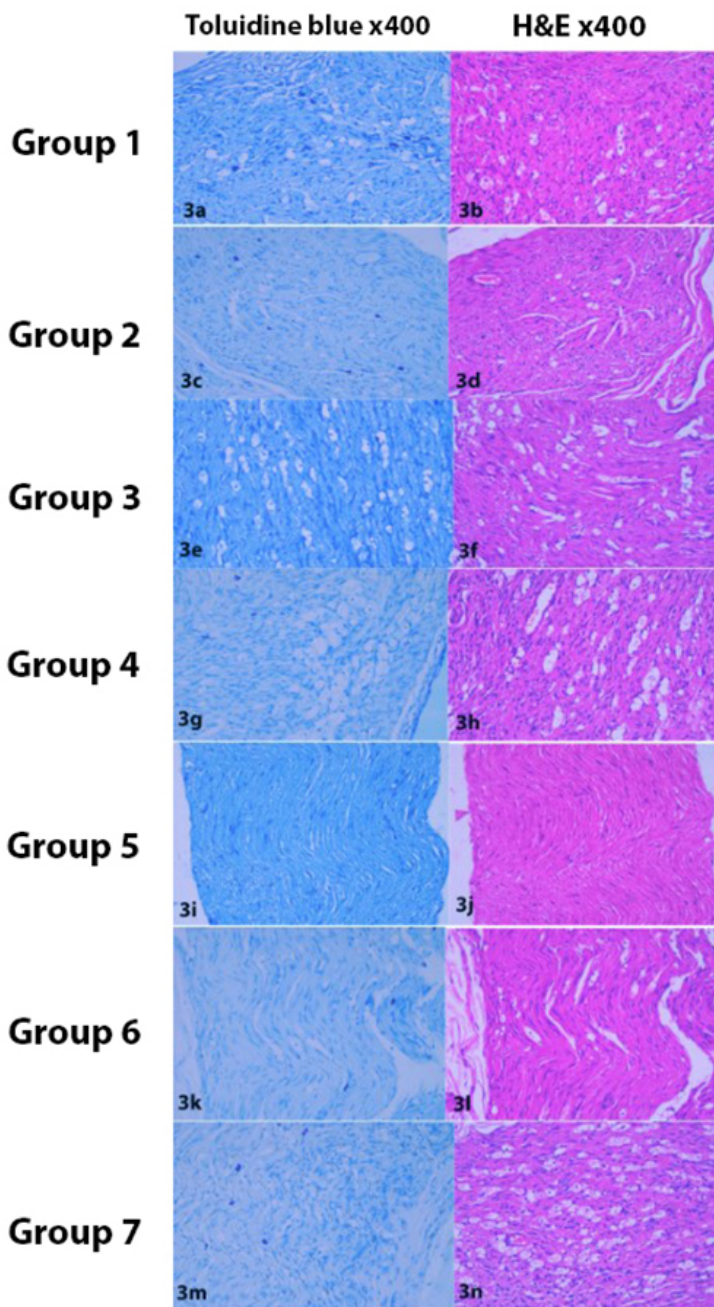| Groups	Percantage of damage	Severe of damage
Group 1 (Control)	0	No
Group 2 (Anastomosis + Control)	100	Severe
Group 3 (Crushing + Control)	70	Moderate
Group 4 (Anastomosis + Magnetotherapy)	50	Moderate
Group 5 (Anastomosis + Bioresonance)	80	Severe
Group 6 (Crushing + Magnetotherapy)	25	Light
Group 7 (Crushing + Bioresonance)	70	Moderate

Fig. 3. Normal histological features of nerve tissue were observed in the sections of group 1. (Toluidine blue x400, 3a) (H&E x 400, 3b). Significant cellularity, oedema and degeneration are observed in the sections of group 2. (Toluidine blue x 400, 3c) (H&E x 400, 3d). Increased cellularity, degeneration and oedema are observed in the sections of group 3. (Toluidine blue x 400, 3e) (H&E x400, 3f). The sections observed a slight increase in cellularity and mild degeneration in a few foci in the sections of group 4. (Toluidine blue x400, 3g) (H&E x 400, 3h). Significant cellularity and local degeneration are observed in the sections of group 5. (Toluidine blue x 400, 3i) (H&E x400, 3j). The sections observe a slight increase in cellularity and local degeneration in the sections of group 6. (Toluidine blue x 400, 3k) (H&E x 400, 3l). Increased cellularity, degeneration and oedema are observed in the sections of group 7. (Toluidine blue x 400, 3m) (H&E x 400, 3n).

DISCUSSION

Besides the surgical difficulty and the inadequacy of adequate technical feasibility for the recovery of peripheral nerves, the functionality of the results is also unsatisfactory. Only about 10 % of the patients' peripheral nerves can be healed (Frostick *et al*., 1998; Scholz *et al*., 2009; Sinis *et al*., 2011). The success of the treatment can be evaluated based on the functional (Canè *et al*., 1993; Assiotis *et al*., 2012), neurological and histomorphological evidence shown in the study (Wilson & Jagadeesh, 1976; Ito & Bassett, 1983).

Our study found a statistically significant difference between the crushing damage and magnetotherapy group and the crushing control group based on functional, neurological and histopathological examinations. In a study, it was found that acetylcholine esterase activity increased in the endplate and myelination in the group that applied a pulsed magnetic field for 6 hours daily for 4 weeks compared to the control group (Cadossi *et al*., 2020). It has been discussed that the increase in myelination may be the long-term pulsed magnetic field in another sciatic nerve damage model (Mert *et al*., 2017). In a study by Güven *et al*. (2005), it was observed that signal transmission and ion channels were renewed over time in the group that received magnetic therapy when crushing damage was created in the sciatic nerve treated with pulsed magnetic field therapy for 15 and 38 days compared to the control group (Gunay & Mert, 2011).

During the experiment, rats treated with magnetic fields improved walking and stepping on their damaged feet. These improvements are thought to be due to increased myelination and the renewal of ion channels. In the behavioural tests, we observed that the groups that received magnetic field therapy returned quite a good gait and pain sensations compared to the control group. In addition, according to the EMG and pathology results, when the magnetic field applied groups were compared with the control group, it was found that there was an increase in electrical activity and a significant difference in histopathological images. It is anticipated that these improvements may result from biochemical processes, healing of membrane damage and regeneration of the sheath.

In a peripheral nerve damage study, low-frequency pulsed electromagnetic field (PEMF) treatment was applied to rats with crushing damage. When the PEMF treatment group was compared with the control group, no significant difference was observed in either the EMG or histological results (Sisken *et al*., 1989). In a study by Hong *et al*. (1986), it was shown by EMG tests that the magnetic field applied at 1.2 Tesla power caused an increase in the tail excitability of rats, and it could be a possible treatment method for nerve regeneration. In addition, PEMF treatment was applied for 38 days in rats with crushing damage, but in the EMG tests, no significant difference was observed when crushing control and crushing+PEMF treatment were compared (Gunay & Mert, 2011). In an experimental study by Rusovan *et al*. (1992), it was proven that the frequency-dependent electromagnetic field applied to rats with sciatic nerve damage was effective on nerve regeneration.

In a study by Liu *et al*. (2022), only magnetic fields applied to red blood cells without surgical intervention were found to stimulate axonal growth. In vitro studies with Fe3O4@PLGA RBC-like magnetic particles have shown that they increase cell viability. A study has shown that Truncated-waveform magnetic stimulation systems can improve nerve regeneration in rats with peripheral nerve damage and have lowering effects on vagal nerve stimulation. In another study, magnetic field application reduced epileptic attacks in rats (Kagan *et al*., 2019). This study found no significant behavioural, neurological or histopathological difference between the crushing and anastomosis groups treated with bioresonance treatment and the control group. In a study, it has been shown that if the bioresonance rises to a frequency higher than the bioresonance of the relevant tissue, it may cause damage to the nerve fibres as a result of a series of electrophysiological processes, and facial pain may increase due to damage to the trigeminal nerve. Bioresonance therapy increased the thiol groups' content and normalised the superoxide dismutase and glutathione peroxidase activities. However, catalase activity remained above control. Changes in the lymphocyte antioxidant system indicate that bioresonance therapy activates nonspecific protective mechanisms in patients with rheumatoid arthritis (Islamov *et al*., 2002). These results may indicate that we could not effectively use the frequency of bioresonance therapy, which we applied as a treatment in our study.

CONCLUSIONS

We can conclude that magnetic field treatment is effective in the sciatic nerve injury model created by crushing and anastomosis. This result is demonstrated by the behaviour performed, EMG and histopathology. It was concluded that the frequency of bioresonance therapy did not have a therapeutic effect. More studies are needed to optimize the magnetic field therapy and to reveal an entire physiopathological mechanism with further molecular tests.

TAS, A.; NALCI, K. A.; SINCAN, S.; ÖZDEMIR, H.; ÜSTÜN, R.; ARAS, I.; ÇATALKAYA, E.; SEKER, A.; AYCAN, A.; AYCAN, N.; GÜRSOY, G. T. & TUNCER, M. C. Investigación de los efectos neurorregenerativos de biorresonancia y magnetoterapia en ratas inducidas por daño del nervio ciático. *Int. J. Morphol., 41(4)*:1184-1190, 2023.

RESUMEN: El daño a los nervios periféricos es un problema clínico importante que puede conducir a complicaciones graves en los pacientes. En cuanto a la regeneración de los nervios periféricos, es crucial utilizar los nervios de los animales de experimentación y diferentes métodos de evaluación. La sutura epineural o perineural es el gold estándar en el tratamiento de lesiones del nervio ciático, pero la reparación del nervio a menudo no tiene éxito. Este estudio tuvo como objetivo investigar los efectos neuroregenerativos de la magnetoterapia y la biorresonancia en animales de experimentación con daño del nervio ciático. En el estudio, 24 ratas hembras Wistar se dividieron en 7 grupos (n=6) de la siguiente manera: Grupo 1 (Control), Grupo 2 (Control de axonotmesis), Grupo 3 (Control de anastomosis), Grupo 4 (Axonotmesis + magnetoterapia), Grupo 5 (Anastomosis + magnetoterapia), Grupo 6 (Axonotmesis + biorresonancia), Grupo 7 (Anastomosis + biorresonancia). Se aplicaron durante 12 semanas tratamientos de magnetoterapia y biorresonancia. Las pruebas de comportamiento y las pruebas de EMG se realizaron al final de la semana 12. Luego se sacrificaron las ratas y se realizó una evaluación histopatológica. El nivel de significación estadística se tomó como 5 % en los cálculos, y se utilizó el programa de paquete estadístico SPSS (IBM SPSS para Windows, ver.21). Se obtuvieron resultados estadísticamente significativos en pruebas de comportamiento animal, EMG y grupos de patología tratados con magnetoterapia. No hubo diferencia estadísticamente significativa en los grupos con tratamiento de biorresonancia en comparación con los grupos controles. La actividad muscular y la reparación nerviosa, se produjeron en animales de experimentación con daño nervioso periférico agudo, debido a 12 semanas de magnetoterapia.Estudios adicionales deberían respaldar estos resultados.

PALABRAS CLAVE: Biorresonancia; Electromiografía; Magnetoterapia; Regeneración nerviosa; Nervio ciático.

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