

The Role and Mechanism of Aspirin Combined with Rehabilitation Training in the Repair of Sciatic Nerve Injury and the Changes in the *Schwannocytus* (Schwann Cells) in Rats

Rol y Mecanismo de la Aspirina Combinados con Entrenamiento de Rehabilitación en la Reparación de la Lesión del Nervio Ciático y los Cambios en los Schwannocitos (Células de Schwann) en Ratas

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SUMMARY: This study investigated the role and mechanism of aspirin combined with rehabilitation training in the nerve injury repair and Schwann cell changes in rats with sciatic nerve injury. Totally, 120 male healthy SD rats were randomly divided into sham, model, aspirin, and aspirin + rehabilitation groups, with 30 rats in each group. The sciatic nerve function index (SFI), photothermal pain tolerance threshold and inclined plane test results at 4, 6, and 8 weeks after operation were compared. The distance of sensory nerve regeneration and the expression of S100B protein in Schwann cells were analyzed. Compared with the sham group, the SFI of the model, aspirin, and aspirin+rehabilitation groups were significantly lower at 4, 6, and 8 weeks after operation. However, the aspirin and aspirin+rehabilitation groups had significantly higher SFI than the model group. The SFI at 6 and 8 weeks after operation was higher in the aspirin+rehabilitation group than that in the aspirin group ($P<0.05$). The photothermal pain tolerance threshold of the sham, aspirin, and aspirin+rehabilitation groups were significantly higher than those of the model group at 4, 6, and 8 weeks after operation ($P<0.05$). The inclination angles of the model, aspirin, and aspirin+rehabilitation groups were significantly lower than those of the sham group at 4, 6, and 8 weeks after operation, and the inclination angle of the aspirin+rehabilitation group was significantly higher than that of the model and aspirin groups ($P<0.05$). The sensory nerve regeneration distance in aspirin and aspirin+rehabilitation groups was higher than that in the sham and model groups ($P<0.05$). The expression of S100B protein in the aspirin and aspirin+rehabilitation groups was higher than that in the model group ($P<0.05$). Aspirin combined with rehabilitation training can promote the functional recovery of sciatic nerve injury, and the mechanism may be related to the increase of the expression of S100B protein in Schwann cells.

KEY WORDS: Aspirin; Rehabilitation training; Sciatic nerve injury; Rats; *Schwannocytus*; Schwann cells.

INTRODUCTION

Sciatic nerve injury is a relatively common type of peripheral nerve injury, in which there are morphological and functional damages of peripheral nerve. Its pathogenesis involves many factors, such as autoimmune, chemical, physical, and biological factors (Yuan *et al.*, 2021). Some scholars believe that Schwann cells have a direct impact on the internal environment of nerve regeneration and repair in patients with peripheral nerve injury (Liu *et al.*, 2019). Early diagnosis and treatment is the key to improving peripheral nerve injury. It is shown that aspirin can promote the repair of nerve function after nerve injury and improve motor function (Zhang *et al.*, 2021). However, the overall effect of

drug therapy alone is not ideal. Wallerian degeneration occurs at the distal end of a nerve fiber in the early stage after peripheral nerve injury (Arzillo *et al.*, 2014). During this process, the distal myelin and axons are structurally altered within a few hours after injury and gradually decompose within 2-3 days. After 5-6 days, phagocytic cells increase in number, and remove the damaged myelin and axons from the lesion (Bhatia *et al.*, 2000). At 1 week after injury, the repair begins with the proximal axon sprouting and gradually growing into a distal effector at a rate of 1-2 mm/d, and eventually the nerve function is recovered (Blanquie & Bradke, 2018). Schwann cells form a new myelin sheath

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under the effect of nerve growth factors and neurotrophic factors and promote the repair and regeneration of injured nerves. Therefore, changes in nerve growth factors and neurotrophic factors within 7 days after peripheral nerve injury can affect injury progression and repair (Boyd & Gordon, 2003; Blaser *et al.*, 2016).

Rehabilitation training is very important for patients with sciatic nerve injury. It can relieve the adhesion of peripheral nerves, promote the improvement of nerve function, and reduce the risk of muscle atrophy (Capoccia *et al.*, 2014; Cen *et al.*, 2017). At present, there are few reports on the effect and mechanism of aspirin combined with rehabilitation training in sciatic nerve injury. Herein, we assessed the effects of aspirin combined with rehabilitation training on the repair of sciatic nerve injury and on Schwann cells in rats. The possible underlying mechanisms were analyzed and discussed. Our findings may shed light on the pathogenesis of sciatic nerve injury and may provide alternative ways for the treatment of sciatic nerve injury.

MATERIAL AND METHOD

Animals. Healthy SD rats (n=120, male, aged 4-6 weeks) were purchased from the Animal Experiment Center of Xinjiang Medical University. They were kept in standard conditions and acclimated for 1 week before experiments. All animal experiment procedures are approved by the Ethics Committee of the Second Affiliated Hospital of Xinjiang Medical University.

Establishment of sciatic nerve injury model. The sciatic nerve injury model was established as previously described (Bucan *et al.*, 2019). Briefly, after fasting for 4 h, the rats were anesthetized. A 4 cm longitudinal incision was made on the lateral skin of the left hind limb. Then, the sciatic nerve was fully exposed and clamped by hemostatic forceps for about 60 s. The color of the sciatic nerve at the clamped site changed. During the operation, the tissues around the nerves were protected. Finally, the wound was washed with normal saline and sutured with absorbable suture. For sham operation, the sciatic nerve was exposed, but not clamped.

Animal grouping and treatment. SD rats were randomly divided into sham, model, aspirin, and aspirin + rehabilitation groups, with 30 rats in each group. The sciatic nerve injury model was established in model, aspirin, and aspirin + rehabilitation groups. Meanwhile, rats in sham group received sham operation. For treatment, rats in aspirin + rehabilitation group were given Aspirin (60 mg/kg; Xuzhou Enhua Pharmaceutical Group Co., Ltd., China) by gavage

from the day of operation for 7 days (1 time/day) and rehabilitation therapy. During the early stage of injury (within 7 days), passive joint motion of the affected limb was 3-5 times a day. After passive motion for 7 days, both passive and active joint motion was conducted 2 times per day and each time lasted for 15 min. The rehabilitation intervention lasted for 4 courses (8 weeks) with 2 weeks as a course of treatment. Rats in the aspirin group received Aspirin (60 mg/kg) by gavage from the day of operation for 7 days (1 time/day). The sham and model groups were given equal volume of normal saline by gavage for 7 days (1 time/day). In the following weeks, no other specific treatment was performed in the sham, model, and aspirin groups.

Sciatic functional index (SFI). At 4, 6, and 8 weeks after operation, SFI was measured. Briefly, self-made SFI walking box was used. To obtain footprints of rats, the red ink was painted to their feet. Three clear footprints were selected and the following parameters were measured: the footprint length of experimental (EPL) and non-operational foot (NPL), the toe spread of experimental (ETS) and non-operational foot (NTS), and the inter toes distance of experimental (EIT) and non-operational foot (NIT). The SFI was calculated with the following formula: $SFI = -38.3(EPL - NPL) / NPL + 109.5(ETS - NTS) / NTS + 13.3(EIT - NIT) / NIT - 8.8$ (Yan *et al.*, 2018).

Photothermal pain tolerance threshold. The photothermal pain tolerance threshold to radiant heat was detected at 4, 6, and 8 weeks after operation with BW-Plantar390 Plantar Test (BIO EXCELLENCE INTERNATIONAL Tech Co., Ltd, Beijing, China). In detail, the radiant thermal stimulator was focused at about 1/3 of the plantar surface. The time from heat stimulation to the spontaneous lifting of rat limb was defined as the photothermal pain tolerance threshold (Zhu *et al.*, 2014). Three independent tests were performed and the mean value of them was recorded.

Inclined plane test. As previously described (Sun *et al.*, 2017), the inclined plane test was performed at 4, 6, and 8 weeks after operation. Briefly, the rats were placed on the self-made plate (50 cm × 30 cm), one end of which was fixed on the table, with the hip facing down and the head facing up. When the rat was in a quiet state, the plate was tilted, and the tilt degree was slowly increased until the rat cannot stay on the plate. The angle of inclination at this time was measured. The mean value of three measurements was recorded.

Sensory nerve regeneration distance. After regular anesthesia, the sciatic nerve on the operative side of the rats was exposed. Under microscope, the sciatic nerve was clamped from 2.5 cm of the distal end of the anastomosis to the proximal end at a distance of 0.2~0.3 mm per interval. The clamp was stopped when there was dorsal muscle

contraction. The distance from the stop point to the anastomosis was measured with vernier caliper and defined as sensory nerve regeneration distance, according to previous description (Lin *et al.*, 2019a).

Immunohistochemistry. The rats were sacrificed at the 8th week. The sciatic nerve samples were collected and fixed with 4 % paraformaldehyde. Expression of S100B protein was detected in sciatic nerve samples using immunohistochemical kit (Maxin Biotechnology Development Co., Ltd., Fuzhou, China). The brown and tan staining in cells were considered as positive S100B expression. Five random fields were selected under high magnification (× 400). The staining was graded as follows: no staining or slight staining of cells and/or stroma (grade 1); light staining of cells and/or stroma, with small foci (grade 2); medium intensity of staining, with patchy foci (grade 3); and, deep and widely distributed staining (grade 4).

Statistical analysis. SPSS20.0 software was used data analysis. The counting data is expressed as frequency (rate) (n (%)) and was compared with χ^2 test. The measurement data of normal distribution is presented as mean \pm standard deviation. The comparison among multiple groups was

performed by one-way or repeated measures ANOVA followed by LSD-t test. $P < 0.05$ indicated statistically significant difference.

RESULTS

Increased SFI in aspirin+rehabilitation group. As shown in Table I, the SFI of the model group, aspirin group, and aspirin+rehabilitation group at 4, 6, and 8 weeks after operation were significantly lower than that of the sham group ($P < 0.05$). Compared with the model group, the aspirin group and aspirin+rehabilitation group had significantly higher SFI ($P < 0.05$). Additionally, the SFI of aspirin+rehabilitation group was significantly higher than that of aspirin group at 6 and 8 weeks after operation ($P < 0.05$). This result showed that the SFI in the aspirin+rehabilitation group increased more significantly. Comparison of photothermal pain tolerance threshold. The photothermal pain tolerance threshold of the model, aspirin and aspirin+rehabilitation groups at 4 and 6 weeks after operation was significantly lower than that of sham group ($P < 0.05$) (Table II). The photothermal pain tolerance

Table I. Comparison of SFI.

Group (n=30 per group)	Week 4	Week 6	Week 8
Sham group	-5.36 \pm 0.51	-4.84 \pm 0.87 Δ	-3.98 \pm 0.63 Δ
Model group	-38.22 \pm 6.56 Δ	-39.04 \pm 6.79 Δ	-35.09 \pm 4.89 Δ
Aspirin group	-32.89 \pm 9.96 Δ [▲]	-30.25 \pm 6.35 Δ [▲]	-25.59 \pm 5.05 Δ ^a ^b [▲]
Aspirin + rehabilitation group	-30.26 \pm 6.05 Δ [▲]	-26.87 \pm 3.08 Δ ^a [▲] [♯]	-18.00 \pm 2.07 Δ ^a ^b [▲] [♯]

Note: Compared with week 4 within groups, ^a $P < 0.05$; Compared with week 6 within groups, ^b $P < 0.05$; Compared with the sham group at the same time point, $\Delta P < 0.05$; Compared with the model group at the same time point, [▲] $P < 0.05$; Compared with aspirin group at the same time point, [♯] $P < 0.05$.

Table II. Comparison of photothermal pain tolerance threshold (s).

Group (n=30 per group)	Week 4	Week 6	Week 8
Sham group	8.68 \pm 0.51	9.67 \pm 0.42 ^a	11.37 \pm 0.87 ^a
Model group	6.34 \pm 0.48 Δ	7.64 \pm 0.27 ^a Δ	8.13 \pm 0.34 ^a ^b Δ
Aspirin group	7.42 \pm 0.45 Δ [▲]	8.85 \pm 0.38 ^a Δ [▲]	11.04 \pm 0.67 ^{ab} Δ [▲]
Aspirin + rehabilitation group	7.65 \pm 0.40 Δ [▲]	8.96 \pm 0.31 ^a Δ [▲]	11.16 \pm 0.55 ^{ab} Δ [▲]

Note: Compared with week 4 within groups, ^a $P < 0.05$; Compared with week 6 within groups, ^b $P < 0.05$; Compared with the sham group at the same time point, $\Delta P < 0.05$; Compared with the model group at the same time point, [▲] $P < 0.05$; Compared with aspirin group at the same time point, [♯] $P < 0.05$.

Table III. Comparison of angle of inclination (°).

Group (n=30 per group)	Week 4	Week 6	Week 8
Sham group	43.67 \pm 1.13 ^o	48.27 \pm 1.67 ^o ^a	51.08 \pm 1.64 ^o ^{ab}
Model group	35.92 \pm 1.10 ^o Δ	38.12 \pm 1.45 ^o Δ	40.30 \pm 1.08 ^o ^{ab} Δ
Aspirin group	38.64 \pm 0.57 ^o Δ [▲]	41.36 \pm 0.81 ^o Δ ^a [▲]	44.12 \pm 1.30 ^o ^{ab} Δ [▲]
Aspirin + rehabilitation group	40.64 \pm 0.98 ^o Δ ^a [▲] [♯]	44.58 \pm 1.64 ^o Δ ^a [▲] [♯]	47.51 \pm 1.17 ^o ^{ab} Δ [▲] [♯]

Note: Compared with week 4 within groups, ^a $P < 0.05$; Compared with week 6 within groups, ^b $P < 0.05$; Compared with the sham group at the same time point, $\Delta P < 0.05$; Compared with the model group at the same time point, [▲] $P < 0.05$; Compared with aspirin group at the same time point, [♯] $P < 0.05$.

threshold of the aspirin group and aspirin+rehabilitation group was significantly higher than that of model group ($P<0.05$). The photothermal pain tolerance threshold of the sham group, aspirin group and aspirin+rehabilitation group at 8 weeks after operation was significantly higher than that of model group ($P<0.05$). This data revealed that the photothermal pain tolerance threshold in the aspirin+rehabilitation group was significantly improved.

Comparison of angle of inclination. The angle of inclination was measured with the inclined plane test. Compared with the sham group, the model group, aspirin group, and aspirin+rehabilitation group had significantly

lower angle of inclination at 4, 6, and 8 weeks after operation ($P<0.05$) (Table III). Additionally, the aspirin+rehabilitation group had significantly higher angle of inclination than the model group and aspirin group ($P<0.05$). Thus, the angle of inclination in the aspirin+rehabilitation treatment group improved more significantly.

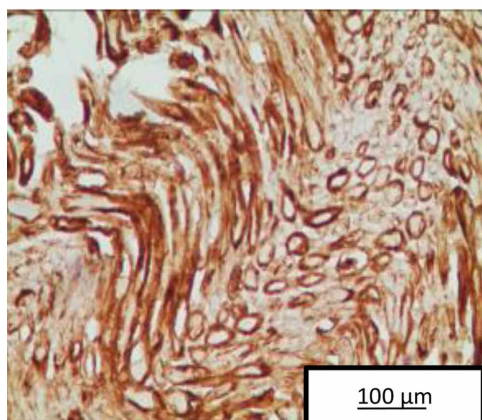
Comparison of sensory nerve regeneration distance and S100B protein expression. To assess nerve regeneration, the sensory nerve regeneration distance was compared. Moreover, immunohistochemistry detected S100B protein expression (Fig. 1). As shown in Table IV, the regeneration distance of sensory nerve and the positive expression of

Table IV. Comparison of sensory nerve regeneration distance (mm) and S100B protein expression (%).

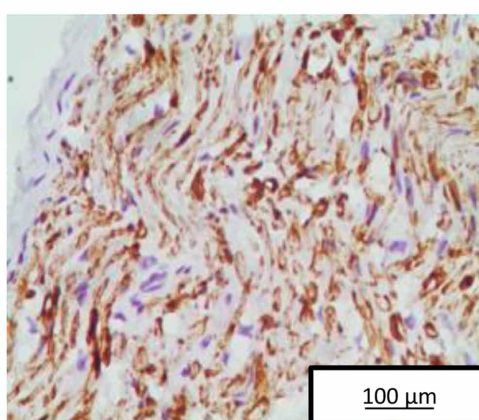
Group (n=30 per group)	Sensory nerve regeneration distance (mm)	Positive S100B protein percentage (%)
Sham group	17.44±0.43	89.25±2.96
Model group	15.61±1.18 [△]	80.62±2.26 [△]
Aspirin group	22.89±0.80 ^{△▲}	86.57±3.55 ^{△▲}
Aspirin + rehabilitation group	23.09±0.61 ^{△▲}	86.42±5.94 ^{△▲}

Note: Compared with the sham group, [△] $P<0.05$; Compared with the model group, [▲] $P<0.05$; Compared with aspirin group, [▴] $P<0.05$.

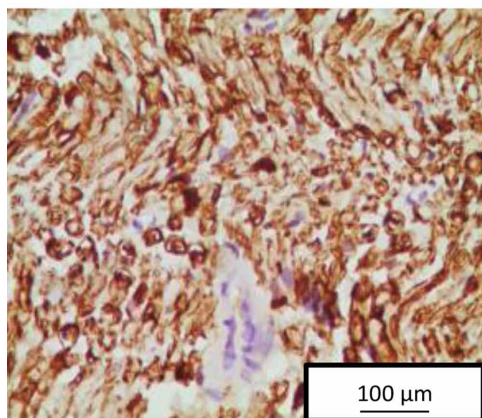
Sham group



Model group



Aspirin group



Aspirin+rehabilitation group

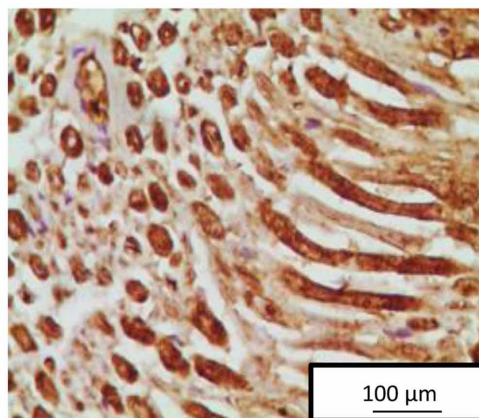


Fig. 1. Immunohistochemical analysis of S100B protein. Positive S100B expression was shown as brown and tan staining. Representative immunohistochemical images of each group were shown. Magnification X 400. Scale bar: 100 μm.

S100B protein in the aspirin group and aspirin+rehabilitation group were significantly higher than those in sham group and model group ($P < 0.05$). Therefore, aspirin combined with rehabilitation training can effectively improve the nerve function in rats with sciatic nerve injury.

DISCUSSION

Sciatic nerve injury can cause manifestations such as pain in the innervated area, sensory dysfunction, and dyskinesia, which have a great impact on the quality of life of patients. Previous studies (Duarte-Moreira *et al.*, 2018; Costales *et al.*, 2019) believed that surgery, physical therapy, chemotherapy, etc. can promote the functional recovery of injured nerves. The mechanism includes improving the level of neurotrophic factors, and improving the function of Schwann cells (Guan *et al.*, 2019). However, the effect of any single therapy on sciatic nerve injury is very limited, and the combined therapy has more advantages (Huang *et al.*, 2018; Ibarra-Lara *et al.*, 2019). Studies from Li *et al.* (2019) and Lin *et al.* (2019b) have shown that oxygen free radicals are released during neurological damage, which can cause apoptosis and necrosis of cells, and aggravate neurological damage. Aspirin can clear oxygen free radicals, reduce lipid peroxidation, and improve neurological damage caused by neurotoxicity (Malik & Kanneganti, 2018). In addition, rehabilitation training plays an important role in sciatic nerve injury and can promote the functional recovery of damaged nerves (Zhang *et al.*, 2019). We suppose that the combination of aspirin and rehabilitation training may benefit the patients with sciatic nerve injury.

In this study, we found that the SFI of the aspirin group and the aspirin+rehabilitation group increased at 4, 6 and 8 weeks after operation, and the more significant effect was observed in the aspirin+rehabilitation group. Furthermore, the photothermal pain tolerance threshold, inclination angle and sensory nerve regeneration distance of the aspirin+rehabilitation group were also significantly improved. These results indicate that aspirin combined with rehabilitation training can effectively improve the neural function, and improve the pain tolerance threshold and motor ability of rats with sciatic nerve injury. The specific mechanism underlying the effect of aspirin on sciatic nerve injury has not been fully clarified. A previous animal study indicated that aspirin could improve the nerve injury after cerebral ischemia and reperfusion in rats by regulating the discoidin domain receptor 1, suggesting that aspirin has a protective effect on neural function (Rashidiani-Rashidabadi *et al.*, 2019). In addition, aspirin is a

vasoactive drug, which can inhibit platelet aggregation, improve microcirculation, promote nutrition supply, and correct cell hypoxia of the damaged nerve, which is conducive to neural function repair (Cui *et al.*, 2018; Sun *et al.*, 2022). Rehabilitation training can promote the metabolism and blood microcirculation of motor tissues, improve muscle strength and endurance, enhance muscle excitability, and is beneficial to the recovery of neural function (Cui & Hu, 2019; Chen *et al.*, 2022). Therefore, we suppose that our results may be related to the improvement of microcirculation of injured nerve by aspirin and the repair of nerve function by rehabilitation training. On the one hand, the combination of aspirin and rehabilitation can improve the blood supply of tissues and promote the regeneration of nerve function. On the other hand, it can improve the nerve tension and improve the curative effect.

Schwann cells, as a kind of unique glial cells in the peripheral nervous system, play an important role in the development of peripheral nerve and the maintenance of peripheral nerve function (Wang *et al.*, 2019). They can promote the secretion of active substances, and can induce and regulate myelin sheath formation and axon regeneration (Lu *et al.*, 2017). In addition, they can also produce cell adhesion molecules, form connections with adjacent axons, and promote the proliferation of adjacent axons, which are beneficial to nerve regeneration and functional repair (Kang *et al.*, 2019; Duman *et al.*, 2020). S100B protein is only expressed in Schwann cells, and with the increased proliferation of Schwann cells, its level will be correspondingly increased, which can reflect the changes of Schwann cells (Li *et al.*, 2020). Herein, our results showed that, compared with the model group, the expression level of S100B protein in the aspirin group and the aspirin+rehabilitation group was up-regulated. This suggests that aspirin may promote the improvement of neuronal function and protect nerve cells and functions by up regulating the expression of S100B protein. It has been reported that aspirin could promote the proliferation of Schwann cells, enhance the activity of adenosine triphosphate enzyme, promote the development of motor neurons, cortical neurons, etc., and is conducive to the survival of neurons (Zhang *et al.*, 2020). However, the specific mechanism of up-regulating S100B protein expression by aspirin is still unclear, which may be related to its nutritional effect on nerve function and repair of nerve injury. Interestingly, we found that the effects of aspirin alone and aspirin+rehabilitation on the photothermal pain tolerance threshold, sensory nerve regeneration distance and S100B protein expression were comparable. However, the overall effect of aspirin+rehabilitation was better, especially on SFI and inclination angle.

This study has some limitations. For example, the sample size was small. Further studies with larger sample sizes are warranted.

To sum up, aspirin combined with rehabilitation training could effectively improve the neural function of rats with sciatic nerve injury and may promote the proliferation of Schwann cells by up-regulating S100B protein expression.

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RESUMEN: En este estudio se investigó el papel y el mecanismo que desempeña la aspirina combinada, con el entrenamiento de rehabilitación en la reparación de lesiones nerviosas y los cambios en los schwannocitos en ratas con lesiones en el nervio ciático. En total, 120 ratas SD macho sanas se dividieron aleatoriamente en cuatro grupos de 30 ratas en cada uno: simulación, modelo, aspirina y aspirina + rehabilitación. Se compararon el índice de función del nervio ciático (SFI), el umbral de tolerancia al dolor fototérmico y los resultados de la prueba del plano inclinado a las 4, 6 y 8 semanas después de la operación. Se analizó la distancia de regeneración del nervio sensorial y la expresión de la proteína S100B en los schwannocitos. En comparación con el grupo simulado, el SFI de los grupos modelo, aspirina y aspirina+rehabilitación fue significativamente menor a las 4, 6 y 8 semanas después de la operación. Sin embargo, los grupos de aspirina y aspirina + rehabilitación tuvieron un SFI significativamente más alto que el grupo modelo. El SFI a las 6 y 8 semanas después de la operación fue mayor en el grupo de aspirina + rehabilitación que en el grupo de aspirina ($P<0,05$). El umbral de tolerancia al dolor fototérmico de los grupos simulado, aspirina y aspirina+rehabilitación fue significativamente mayor que el del grupo modelo a las 4, 6 y 8 semanas después de la operación ($P<0,05$). Los ángulos de inclinación de los grupos modelo, aspirina y aspirina+rehabilitación fueron significativamente menores que los del grupo simulado a las 4, 6 y 8 semanas después de la operación, y el ángulo de inclinación del grupo aspirina+rehabilitación fue significativamente mayor que el de los grupos modelo y aspirina ($P<0,05$). La distancia de regeneración del nervio sensorial en los grupos de aspirina y aspirina+rehabilitación fue mayor que en los grupos simulado y modelo ($P<0,05$). La expresión de la proteína S100B en los grupos de aspirina y aspirina+rehabilitación fue mayor que en el grupo modelo ($P<0,05$). La aspirina combinada con el entrenamiento de rehabilitación puede promover la recuperación funcional de la lesión del nervio ciático, y el mecanismo puede estar relacionado con el aumento de la expresión de la proteína S100B en los schwannocitos

PALABRAS CLAVE: Aspirina; Capacitación en rehabilitación; Lesión del nervio ciático; Ratas; Schwannocitos.

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