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Research Article

Local Calcium Channel Blocker (Nimodipine) and Improvement of Functional Recovery of the Transected Sciatic Nerve after Bridging with Inside-Out Artery Graft

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Abstract

The objective was to assess the effect of locally administered nimodipine on transected peripheral nerve regeneration and functional recovery. Sixty male healthy white Wistar rats were divided into four experimental groups (n = 15), randomly: In transected group (TC), left sciatic nerve was transected and stumps were fixed in the adjacent muscle. In treatment group defect was bridged using an inside-out artery graft (IOAG/Nimodipine) filled with 10 µL nimodipine (100 ng/mL). In artery graft group (IOAG), the graft was filled with phosphate-buffered saline alone. In sham-operated group (SHAM), sciatic nerve was exposed and manipulated. Each group was subdivided into three subgroups of five animals each and regenerated nerve fibers were studied 4, 8 and 12 weeks after surgery. Behavioral testing, biomechanical studies, sciatic nerve functional study, gastrocnemius muscle mass and morphometric indices confirmed faster recovery of regenerated axons in IOAG/Nimodipine than IOAG group ($p < 0.05$). In immunohistochemistry, location of reactions to S-100 in IOAG/Nimodipine was clearly more positive than that in IOAG group. When loaded in an artery graft nimodipine accelerated and improved functional recovery and morphometric indices of sciatic nerve. This may have clinical implications for the surgical management of patients after facial nerve transection.

INTRODUCTION

The outgrowth of regenerating axons of a transected peripheral motor nerve is a slow process. After an initial delay, which is necessary for the cell bodies to compensate for the retrograde effects of axonal transection, the regenerating axonal sprouts cross the site of injury, reach the distal stump, and grow down the nerve to their peripheral terminations [1].

The conduits act to guide axons sprouting from the regenerating nerve end, provide a microenvironment for diffusion of neurotrophic and neurotropic factors secreted by the injured nerve stump, as well as help protect from infiltration of fibrous tissue [2]. An artery graft presents large quantities of laminin and some collagen. These substances are also found in Schwann-cell basal membrane and are reported as axonal outgrowth factors [3-9]. Laminin, one of the main basal membrane components, stimulates neurite outgrowth, induces Schwann-cell mitosis, and plays a fundamental role in peripheral nerve regeneration.[10,11] As well as requiring nerve fiber contact, normal Schwann-cell differentiation requires contact with a connective tissue matrix or some associated material such as collagen [12]. Standard artery graft basal membrane tube diameter is large, and the

contact surface for migrating Schwann cell or axonal outgrowth cone adhesion becomes very small.[9,13] Nevertheless, in inside-out artery grafts, this negative effect might be diminished once the adventitia provides a permissive matrix which increases the contact surface for axons [13].

Nimodipine, a calcium channel blocker, is a US Food and Drug Administration approved drug used to reduce the morbidity and mortality associated with delayed ischemic deficits in patients with subarachnoid hemorrhage. In addition to its activity in the central nervous system, nimodipine has shown promise in multiple rodent models as a possible pharmacologic treatment for facial nerve injury [14-18].

To the best knowledge of the authors, the literature is poor regarding the beneficial local effects of nimodipine on transected sciatic nerve. Aimed to study local effects of nimodipine on sciatic nerve regeneration, a study was designed to determine if local nimodipine could in fact reduce dysfunction after nerve injury in the rat sciatic nerve transection model. Assessment of the nerve regeneration was based on behavioral, biomechanical, functional, histomorphometric and immuohistochemical (Schwann cell detection by S-100 expression) criteria 4, 8 and 12 weeks after surgery.

MATERIALS AND METHODS

Study design and animals

Eighty male Wistar rats weighing approximately 250g were divided into four experimental groups (n = 15), randomly: sham-operation group as normal control (SHAM), transected control (TC), inside –out artery graft (IOAG) and nimodipine treated group (IOAG/Nimodipine). Fifteen rats were used as artery graft donors. Each group was further subdivided into three subgroups of five animals each and studied 4, 8 and 16 weeks after surgery. Two weeks before and during the experiments, the animals were housed in individual plastic cages with an ambient temperature of (23±3) ˚C, stable air humidity and a natural day/night cycle. The rats had free access to standard rodent laboratory food and tap water. All measurements were made by two blinded observers unaware of the analyzed groups.

Surgical procedure

Animals were anesthetized by intraperitoneal administration of ketamine-xylazine (ketamine 5%, 90mg/kg and xylazine 2%, 5mg/kg). The procedure was carried out based on the guidelines of the Ethics Committee of the International Association for the Study of Pain [60]. The University Research Council approved all experiments.

Following surgical preparation in the sham-operation group, the left sciatic nerve was exposed through a gluteal muscle incision and after careful homeostasis the muscle was sutured with resorbable 4/0 sutures, and the skin with 3/0 nylon. In TC group, the left sciatic nerve was transected proximal to the tibio-peroneal bifurcation where a 7mm segment was excised, leaving a 10mm gap due to retraction of nerve ends. Proximal and distal stumps were fixed in the adjacent muscle with 10/0 nylon epineurial suture. No graft was interposed between the stumps. In the IOAG group, a 7 mm nerve segment was resected to produce a 10 mm nerve gap after retraction of the nerve transected ends. The gap was bridged using an artery graft, entubulating 2 mm of the nerve stump at each end. The artery graft was harvested from abdominal aorta of donor animals. The abdominal aorta artery was exposed through a midline abdominal incision and cannulated. Then, a 15 mm segment was harvested on the cannula. Donor animals were sacrificed after graft harvest using a high-dose anesthetic. Harvested grafts were washed in physiological solution and left at room temperature for 40 minutes. A subtle retraction of 1mm was already expected. Each graft was inverted inside-out by pulling it down the cannula with microsurgery tweezers. Allografts did not receive preliminary treatment to reduce their antigenicity. Two 10/0 nylon sutures were used to anchor the graft to the epineurium at each end. In nimodipine treated group (IOAG/Nimodipine) the graft was filled with 10 µl nimodipine (100 ng/mL). The animals were anesthetized and euthanized with transcardiac perfusion of a fixative containing 2% paraformaldehyde and 1%glutaraldehyde buffer (pH 7.4) 4, 8 and 12 weeks after surgery.

Behavioral Testing

Functional recovery of the nerve was assessed using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale for rat hind limb motor function [19]. Although BBB is widely used to assess functional recovery in spinal cord injured animals, however, it has been demonstrated that it could be most useful in assessment of never repair processes in peripheral nerve injuries [20]. Scores of 0 and 21 were given when there were no spontaneous movement and normal movement, respectively. A score of 14 shows full weight support and complete limbs coordination (Table 1). BBB recordings were performed by a trained observer who was blinded to the experimental design. The testing was performed in a serene environment. The animals were observed and assessed within a course of a 4-minute exposure to an open area of a mental circular enclosure. BBB scores were recorded once before surgery in order to establish a baseline control and again weekly thereafter to assess functional recovery during 12 weeks.

Functional assessment of reinnervation

Sciatic functional index (SFI): Walking track analysis was performed 4, 8 12 and 16 weeks after surgery based on the method of others [21]. The lengths of the third toe to its heel (PL), the first to the fifth toe (TS), and the second toe to the fourth toe (IT) were measured on the experimental side (E) and the contralateral normal side (N) in each rat. The sciatic function index (SFI) of each animal was calculated by the following formula:

SFI = -38.3× (EPL-NPL)/NPL+109.5× (ETS-NTS)/NTS +13.3× (EIT-NIT)/NIT-8.8

In general, SFI oscillates around 0 for normal nerve function, whereas around -100 SFI represents total dysfunction. SFI was assessed in the NC group and the normal level was considered as 0. SFI was a negative value and a higher SFI meant the better function of the sciatic nerve.

Static sciatic index (SSI): SSI is a time-saving digitized static footprint analysis described by others [22]. A good correlation between the traditional SFI and the newly developed static sciatic

index (SSI) and static toe spread factor (TSF), respectively, has been reported by others [22]. The SSI is a time-saving and easy technique for accurate functional assessment of peripheral nerve regeneration in rats and is calculated using the static factors, not considering the print length factor (PL), according to the equation:

SSI = [(108.44 × TSF) + (31.85 × ITSF)] − 5.49

Where:

TSF = (ETS-NTS)/NTS

ITSF = (EIT-NIT)/NIT

Like SFI, an index score of 0 was considered normal and an index of −100 indicated total impairment. When no footprints were measurable, the index score of −100 was given.

Electrophysiological assessme: At the end of the study period, following walking track, all animals were subjected to electrophysiological studies using Nacro bio system 320-3760 A trace 80 (USA). Under general anesthesia, the left sciatic nerve was re-exposed by incision of the skin at the previous surgical site. Single electrical pulses at supramaximal intensity were delivered via bipolar electrodes placed in turn at the proximal and distal trunk of the grafted nerve and EMG was recorded by inserting an electrode into the belly of gastrocnemius muscle.

The difference in latency of EMG was measured, and the distance between the proximal and distal sites of stimulation was measured to calculate the conduction velocity across the regenerated tissue cable. On the contra lateral side of each animal similar measurement was made for determination of conduction velocity. The conduction velocity of the bridged nerve was expressed as a percentage of that on the intact side of each animal to cancel off variations between animals (% CVR) [23].

Biomechanical testing: Following electrophysiological assessments the regenerated nerves were harvested and placed in a normal saline bath at room temperature. The samples were then fixed between frozen fixtures in a mechanical apparatus. The TA.XTPlus Texture Analyzer mechanical test device was used for the assessment (Stable Micro Systems, Surrey GU7 1YL, UK). After 5 minutes, the frozen fixtures were tightened to ensure that no slippage occurred during testing. The initial length was set to 10 mm. Each sample was stretched at a constant rate of 1 mm/min. The load and displacement were sampled 5 times per second. Each sample was stretched to complete tensile failure. Samples were kept wet moist during testing using a drop of normal saline solution to the nerve segments.

Muscle mass: Recovery assessment was also indexed using the weight ratio of the gastrocnemius muscles 12 weeks after surgery. Immediately after sacrificing of animals, gastrocnemius muscles were dissected and harvested carefully from intact and injured sides and weighed while still wet, using an electronic balance.

Histological preparation and morphometric studies: Nerve mid-substance in SIL group, nerve mid-substance in nimodipine treated group, midpoint of normal sciatic nerve (Sham) and regenerated mid substance of TC group were harvested and fixed with glutaraldehyde 2.5%. They were post fixed in OsO4 (2%, 2 h), dehydrated through an ethanol series and embedded in Epon. The nerves were cut in 5 µm in the middle, stained with toluidine blue and examined under light microscopy. Morphometric analysis was carried out using an image analyzing software (Image-Pro Express, version 6.0.0.319, Media Cybernetics, Silver Springs, MD, USA). Equal opportunity, systematic random sampling and two-dimensional dissector rules were followed in order to cope with sampling-related, fiber-location-related and fiber-size related biases.[24]

Immunohistochemical analysis

In this study, anti-S-100 (1:200, DAKO, USA) was used as marker for myelin sheath. Specimens were post fixed with 4% paraformaldehyde for 2h and embedded in paraffin. Prior to immunohistochemistry nerve sections were dewaxed and rehydrated in PBS (pH 7.4). Then the nerve sections were incubated with 0.6% hydrogen peroxide for 30 minutes. To block non-specific immunoreactions the sections were incubated with normal swine serum (1:50, DAKO, USA). Sections were then incubated in S-100 protein antibody solution for 1h at room temperature. They were washed three times with PBS and incubated in biotynilated anti-mouse rabbit IgG solution for 1h. Horseradish peroxidase-labelled secondary antibody was applied for 1 h. After that all sections were incubated with 3,3'- diaminobenzidine tetrahydrochloride chromogene substrate solution (DAB, DAKO, USA) for 10 min. The results of immunohistochemistry were examined under a light microscope.

Statistical analysis

The results were expressed as means ± SD. Statistical analyses were performed using PASW 18.0 (SPSS Inc., Chicago, IL, USA). Model assumptions were evaluated by examining the residual plot. Results were analyzed using a factorial ANOVA with two between-subjects factors. Bonferroni test for pairwise comparisons was used to examine the effect of time and treatments. The differences were set at $P< 0.05$.

RESULTS

Behavioral testing

BBB recovery: In order to assess hind limb recovery the open field locomotor was used. Figure 1 shows BBB scores compared to the baseline. All experimental groups, except for sham, showed the greatest degree of functional deficit one week after surgery. The nimodipine treated group showed significant improvement in locomotion of the operated limb compared to the IOAG group during the study period ($P< 0.05$).

Recovery of sciatic nerve function

SFI outcome: Figure 2 shows sciatic function index (SFI) values in all four experimental groups. Prior to surgery, SFI values in all groups were near zero. After the nerve transection, the mean SFI decreased to -100 due to the complete loss of sciatic nerve function in all animals. At the end of the study period, animals of nimodipine group achieved a mean value for SFI of -45.3 ± -2.54 whereas in group IOAG a mean value of -57.3 ± -3.50 was found. The statistical analyses revealed that the recovery of nerve function was significantly ($P < 0.05$) different between IOAG/Nimodipine and IOAG groups and application of

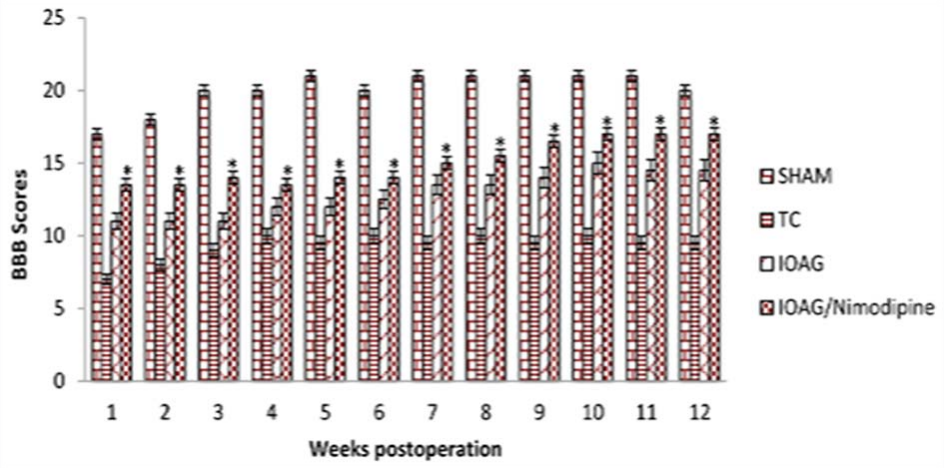

Figure 1 BBB score for all experimental groups. Local administration of nimodipine with artery grafting gave better scores than in IOAG group. Data are presented as mean ± SD. * $P < 0.05$ *vs* IOAG group.

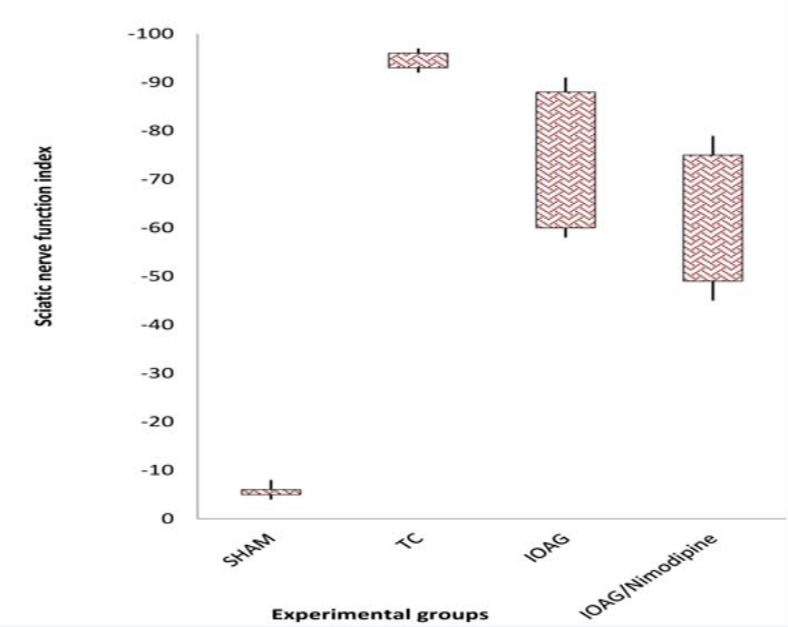

Figure 2 Box-and-whisker plots of sciatic nerve function index values (SFI) in each experimental group during the study period. Local dministration of nimodipine gave better results in functional recovery of the sciatic nerve than in IOAG group.

the nimodipine in artery graft significantly accelerated functional recovery in the course of time.

SSI outcome: Changes in SSI were similar to those observed in SFI, indicating significant deficit following the sciatic nerve transection (Figure 3). Changes in SSI were significant at weeks 4, 8 and 12 of recovery ($P < 0.05$). The contrasts indicate SSI values in group IOAG/Nimodipine at week 12 to differ significantly from those obtained from IOAG, a trend also noticed for SFI ($P < 0.05$).

Electrophysiological measuremen

Figure 4 and 5 show nerve conduction velocity (NCV) along regenerated sciatic nerves in experimental groups. NCV in IOAG/Nimodipine group was significantly higher than that in IOAG group ($P < 0.05$).

Biomechanical measurements

Maximum pull force (F_{max}) of normal sciatic nerve was found to be 5.50 ± 0.40. F_{max} of nerve samples in experimental groups are shown in Table 1. F_{max} in IOAG/Nimodipine group (3.73 ± 0.31) was significantly higher than that in IOAG group (2.59 ± 0.30) ($P < 0.05$). Tensile strength, the amount of force per unit of initial cross-sectional area at tensile failure, was measured based on F_{max} and nerve cross sectional area. 12th week assessment revealed tensile strength of regenerated nerves treated with nimodipine (5.21 ± 0.18) was higher than those in IOAG group (4.00 ± 0.22) ($P < 0.05$). Ultimate strain, the amount of elongation

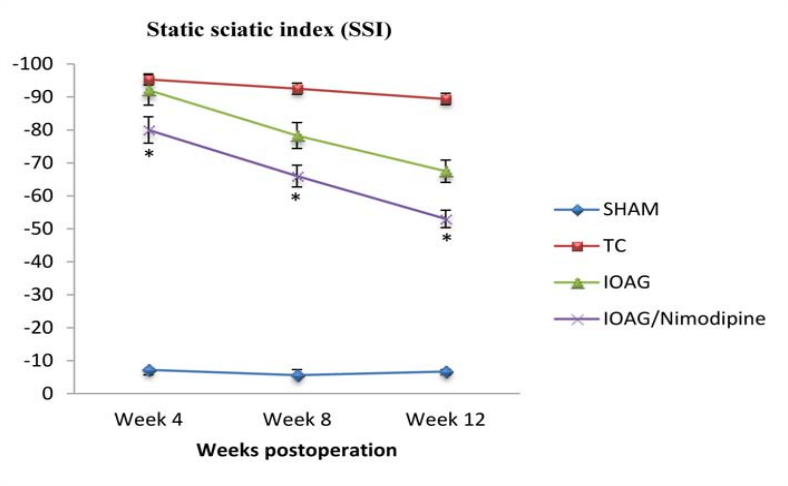

Figure 3 Line graph indicating static sciatic index (SSI) values in each experimental group during the study period. Local administration of nimodipine with artery grafting gave better results in functional recovery of the sciatic nerve than in IOAG group. Data are presented as mean ± SD. * $P < 0.05$ *vs* IOAG group.

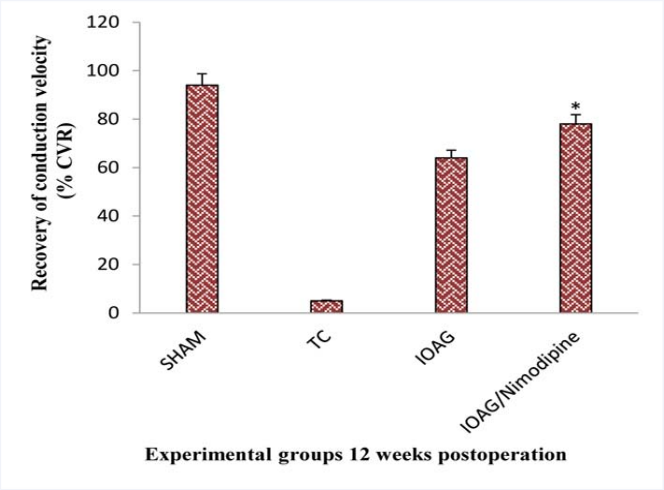

Figure 4 Percentage recovery of conduction velocity in experimental groups. Data are presented as mean ± SD. * $P < 0.05$ *vs* IOAG group.

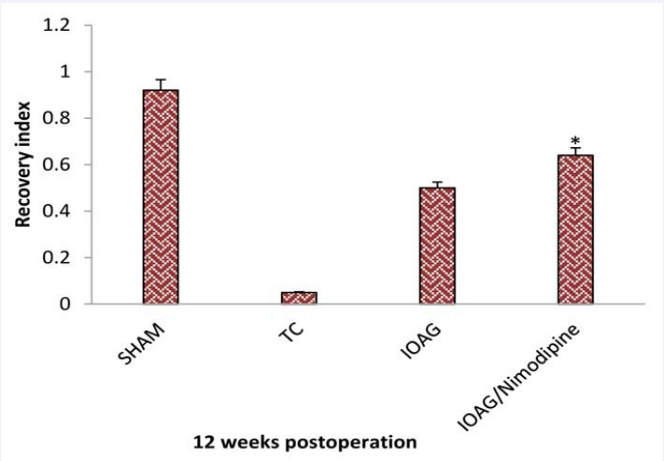

Figure 5 Recovery index in experimental groups. Data are presented as mean ± SD. * $P < 0.05$ *vs* IOAG group.

divided by the initial specimen length achieved at the point of tensile failure, in IOAG/Nimodipine group (0.32 ± 0.02)was significantly higher than that in IOAG group (0.25 ± 0.03) (P < 0. 05). Toughness, reflecting the properties of anti-deformation and anti-fracture of nerve, was determined by the nerve itself and could reflect "looseness" or "toughness" of nerve. Toughness in IOAG/Nimodipine group (0.73 ± 0.22) was significantly higher than that in IOAG group (0.44 ± 0.23) (P < 0. 05).

Muscle mass measurement

The mean ratios of gastrocnemius muscle weight were measured at the end of the study period. There was a statistically significant difference between the muscle weight ratios of the IOAG/Nimodipine and IOAG groups (P < 0.05). The results showed that in the nimodipine treated group, the muscle weight ratio was larger than in the IOAG group, and weight loss in the gastrocnemius muscle was ameliorated by nimodipine local administration (Figure 6).

Histological and Morphometric findings

The nimodipine treated group presented significantly greater nerve fiber, axon diameter, and myelin sheath thickness during study period, compared to IOAG animals (P < 0.05). Sham-operation group presented significantly greater nerve fiber and axon diameter, and myelin sheath thickness compared to IOAG/Nimodipine and IOAG groups animals (Figure 7-10). In case of myelin thickness there was no significant difference between IOAG/Nimodipine and IOAG groups, morphometrically (P>0.05).

Immunohistochemistry

Immunoreactivity to S-100 protein was extensively observed in the cross sections of regenerated nerve segments. The expression of S-100 protein signal was located mainly in the myelin sheath. The axon also showed a weak expression indicating that Schwann cell-like phenotype existed around the myelinated axons (Figure 11). In both IOAG/Nimodipine and IOAG groups, the expression of S-100 and the findings resembled those of the histological evaluations.

DISCUSSION

The results of the present study showed that application of nimodipine in an artery graft resulted in faster functional recovery of the sciatic nerve during the study period. Left gastrocnemius muscle weight was significantly greater in the IOAG/Nimodipine group than in the IOAG group, indicating indirect evidence of successful end organ reinnervation in the nimodipine treated animals. At week 12 quantitative morphometrical indices of regenerated nerve fibers showed significant differences between the IOAG and IOAG/Nimodipine groups, indicating a beneficial effect of topical application of nimodipine on the nerve regeneration. Although both morphological and functional data have been used to assess neural regeneration after induced crush injuries, the correlation between these two types of assessment is usually poor [25-27]. Classical and newly developed methods of assessing nerve recovery, including histomorphometry, retrograde transport of horseradish peroxidase and retrograde fluorescent

labeling do not necessarily predict the reestablishment of motor and sensory functions [27-31]. Although such techniques are useful in studying the nerve regeneration process, they generally fail in assessing functional recovery.[27] Therefore, research on peripheral nerve injury needs to combine both functional and morphological assessment. Castaneda *et al* [32], suggested that arrival of sprouts from the proximal stump at the distal nerve stump does not necessarily imply recovery of nerve function. Information taken from BBB scale may be invaluable in evaluation of peripheral nerve process. Results of the present study showed that the nimodipine treated animals had been improved in locomotion of the operated limb compared to the IOAG group during the study period. Walking track analysis has frequently been used to reliably determine functional recovery following nerve repair in rat models [21,29].

A wide variety of materials have been used to produce nerve guides, including non-biodegradable and biodegradable materials. Because of its inert and elastic properties, the silicon tube was one of the first and most frequently used to bridge the

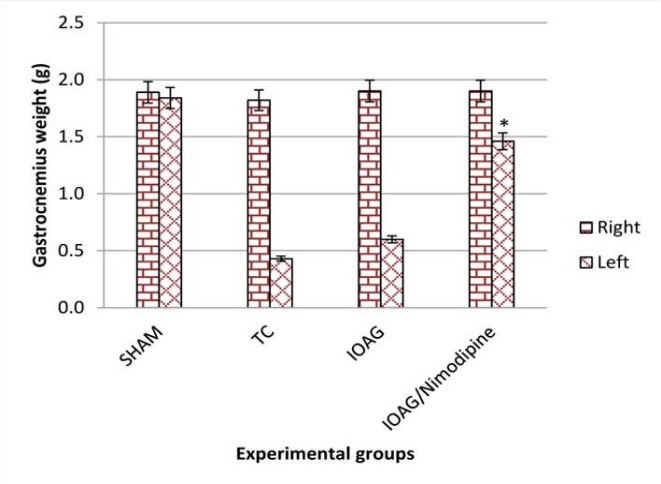

Figure 6 Measurement of gastrocnemius muscle. The gastrocnemius muscle of both sides (injured left and intact right) was removed and weighted in experimental groups 12 weeks after surgery. Data are presented as mean ± SD. * P < 0.05 vs IOAG group.

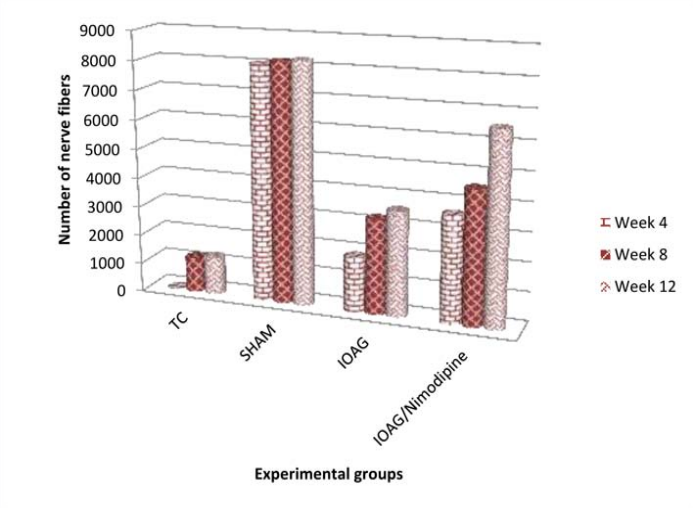

Figure 7 Line graph shows the quantitative results of fiber counting. Both groups of IOAG and IOAG/Nimodipine showed the lower number of fibers than the Sham-operated group even at the end of the study.

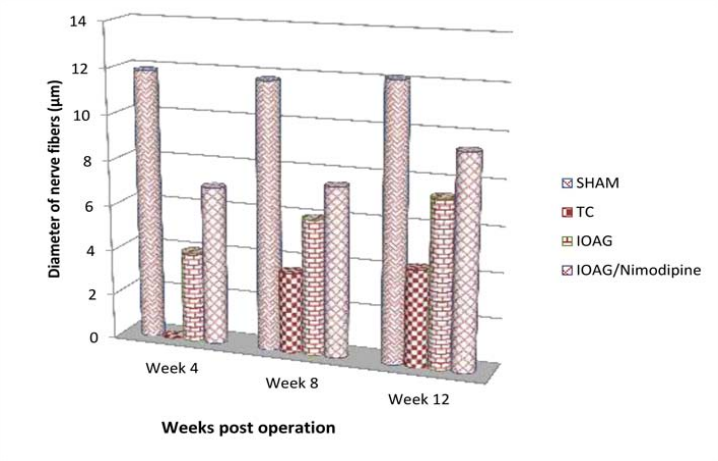

Figure 8 Line graph shows the quantitative results of mean diameter of nerves fibers. Both groups of IOAG and IOAG/Nimodipine showed the lower mean diameter of nerve fibers than the Sham-operated group even at the end of the study.

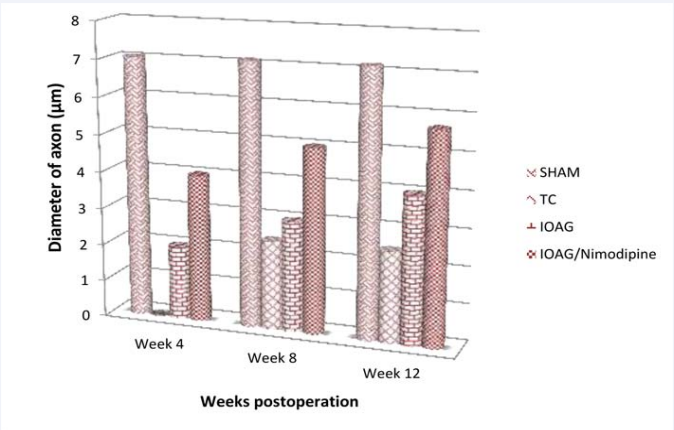

Figure 9 Line graph shows the quantitative results of mean diameter of axon. Both groups of IOAG and IOAG/Nimodipine showed the lower mean diameter of axon than in the Sham-operated group even at the end of the study.

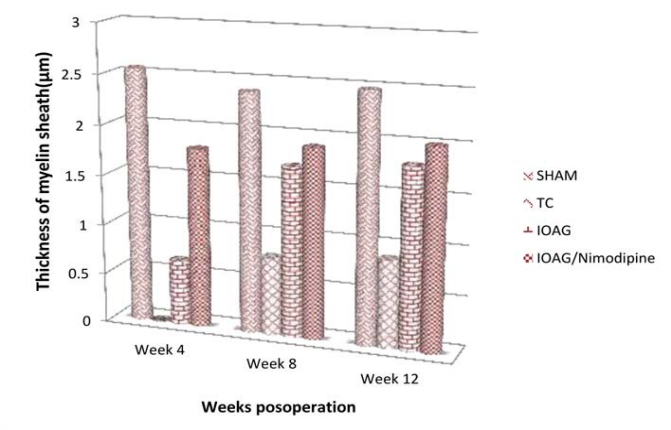

Figure 10 Line graph shows the quantitative results of myelin thickness. Both groups of IOAG and IOAG/Nimodipine showed the lower mean myelin thickness than the Sham-operated group even at the end of the study.

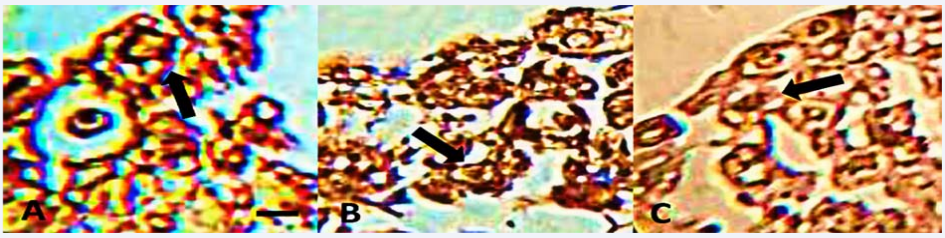

Figure 11 Immunohistochemical analysis of the regenerated nerves 12 weeks after surgery from middle cable (A) SHAM, (B) IOAG, (C) and IOAG/ Nimodipine. There is clearly more positive staining of the myelin sheath-associated protein S- 100 (arrow) within the periphery of nerve, indicating well organized structural nerve reconstruction in nimodipine treated nerve. Scale bar: 10 µm.

transected nerves [33]. Nevertheless, these non-biodegradable tubes induce fibrous capsule formation, leading to chronic nerve compression and an inflammatory response [34]. In order to avoid problems associated with non-degradable guides, recent research has been focused on the production of biodegradable nerve guides [35]. Copolymer of 50% DL-lactide and 50% _ caprolactone (Polyganics B.V.) is a biodegradable guide that is effective in supporting the outgrowth of axons and allows faster axonal regeneration and better recovery [36]. In addition, these guides provide a good tool to administrate factors which can improve the regeneration of injured peripheral nerves in human. However, such a biodegradable guides collapse easily because of their thin walls [37]. Arteries have been experimentally used as grafting tubules and promising results have been achieved [13].

Membranes of the proximal and distal portions of the transected axons are resealed 5-30 min after the transaction [38]. Thereafter, the proximal stump gradually regrows, fostered by the neural cell surface molecule of the transmembrane glycoprotein Ll, nerve cell adhesion molecule (N-CAM), myelinassociated glycoprotein PO, and the extracellular matrix components laminin and tenascin [39]. The regenerating axons are guided by the Schwann cell processes and their growth within the Schwann cell basal lamina tubes is synchronous with the withdrawal and degeneration of the axonal remnants of the distal stump [1,40,41].

Calcium ions play a crucial role in depolarization, outgrowth, excitability, aging, learning, and cell proliferation-in short, neuronal plasticity [42]. It is well known that peripheral nerve injury disrupts the permeability barrier function of the plasma membrane, allowing an influx of Ca2+ down a steep electrochemical gradient between the outside and the inside of the cell [43]. The resultant intracellular free Ca2+ overload triggers a wide array of chain reactions, which eventually may lead to cell death [44,45]. Therefore, an agent preventing the excessive influx of Ca'+ might attenuate cellular damage caused by mechanical neuronal injury and thus improve neuronal recovery [46].

By reducing the amount of calcium influx into the axoplasm of the resprouting nerve fiber, the treatment with nimodipine may provide the necessary optimum level ("set-point") of Ca'+ influx that promotes accelerated growth cone elongation [47-50]. However, it further reduces the buffering capacity of the terminals for Ca'+, which might render their responsiveness to Ca2+ even stronger.

Even though our preliminary study shows the neuroprotective action of local nimodipine in peripheral nerve injuries, determining the molecular mechanisms leading to the neuroprotective action remains needs to be investigated. We have not given the histological and molecular evidence for neuroprotective action of nimodipine. This may be considered as a limitation to our study. Therefore, the authors stress that the aim of the current investigation was to evaluate a single local

dose and clinical treatment potential of nimodipine on transected sciatic nerve regeneration including functional assessments of the nerve repair, a case not considered in previous studies. The results of the present study indicated that a single local administration of nimodipine at the site of transected nerve could be of benefit after artery graft tubulization. Detailed mechanism of neuroprotective action remains to be investigated.

CONCLUSION

The present study demonstrated that a single local application of nimodipine could accelerate functional recovery after transection of sciatic nerve and may have clinical implications for the surgical management of patients after facial nerve transection. Thus, dose–response studies should be conducted for nimodipine to determine the combination of the graft and the compound that achieve maximal efficacy in nerve transection models.

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