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CORRELATION BETWEEN PARAMETERS OF ELECTROPHYSIOLOGICAL, HISTOMORPHOMETRIC AND SCIATIC FUNCTIONAL INDEX EVALUATIONS AFTER RAT SCIATIC NERVE REPAIR

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ABSTRACT - The rat sciatic nerve is a well-established model for the study of recovery from peripheral nerve injuries. Traditional methods of assessing nerve regeneration after nerve injury and repair, such as electrophysiology and histomorphometry, despite widely used in neural regeneration experiments, do not necessarily correlate with return of motor and sensory functions. The aim of this experimental study is to investigate the possible correlation between several parameters of peripheral nerve regeneration after repair of sectioned sciatic nerve in Wistar rat. A two-stage approach was used to obtain 17 parameters after electrophysiological, morphometric and sciatic functional index evaluations. Pearson's correlation analysis was performed between these results. Only two positives correlations between different classes of peripheral nerve assessments were noted, between sciatic functional index and proximal nerve fiber diameter (r=0.56, p<0.01) and between sciatic functional index and distal fiber diameter (r=0.50, p<0.01). The data presented in our study demonstrates that there is a poor correlation between the sciatic functional index and outcome measures of electrophysiological and morphometric evaluations.

KEY WORDS: nerve repair, sciatic functional index, rat sciatic nerve, nerve regeneration, nerve morphometry.

Correlações entre parâmetros obtidos das avaliações eletrofisiológica, histomorfométrica e do índice funcional ciático após o reparo do nervo ciático do rato

RESUMO - O nervo ciático do rato é o modelo mais amplamente utilizado para o estudo da regeneração após uma lesão de nervo. Apesar do uso amplo para a avaliação da regeneração os métodos tradicionais, como a avaliação eletrofisiológica e histomorfométrica, nem sempre apresentam correlações com a recuperação motora e sensitiva. O objetivo deste estudo é investigar as possíveis correlações entre vários parâmetros da regeneração após a secção e reparo do nervo ciático do rato. Foi utilizado um experimento dividido em dois estágios para obter 17 parâmetros após a realização de avaliações eletrofisiológica, histomorfométrica e funcional. A análise das possíveis correlações foi obtida através da aplicação do método de Pearson. Somente duas correlações positivas entre diferentes tipos de avaliações foram obtidas, entre o índice funcional ciático e o diâmetro proximal das fibras (r=0,56, p<0,01) e entre o índice funcional ciático e o diâmetro distal das fibras (r=0,50, p<0,01). Concluímos que as correlações entre diferentes métodos de avaliação da regeneração no nervo ciático do rato são pouco freqüentes.

PALAVRAS-CHAVE: reparo do nervo, índice funcional ciático, nervo ciático do rato, regeneração nervosa, morfometria do nervo.

The rat sciatic nerve is the most used model for evaluation of experimental peripheral nerve regeneration[1,2]. This occurs because rat sciatic nerve regeneration is extremely efficient and fast and this model has a relative low cost[3]. The sciatic nerve is a mixed-function nerve, what makes possible the reproduction of lesions that occur in humans nerves[1]. In addition, this model permits assessment of nerve regeneration after repair using several techniques.

Usually, such assessment includes electrophysiological and histomorphometric studies, measurements of functional recovery and, occasionally, retrograde-

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labeling, immunohistochemistry techniques and other methods[1,3-5]. The most commonly employed methods, the morphometric and the electrophysiological evaluations, may not correlate with function recovery[2,6].

This study reports the correlations of electrophysiological and morphometric assessments of neural regeneration as well as the sciatic functional index after rat sciatic nerve repair. The data were obtained from three separate nerve repair groups: a conventional suture group, a fibrin glue group, and a group in which a combination of both methods was used.

METHOD

Surgical procedure – Eighty-six male Wistar rats, weighing between 250 and 300 g were used. The study was approved by the Ethics Committee of the University of São Paulo Medical School and all procedures followed national animal welfare guidelines. The data used were part of a previously reported study comparing the nerve regeneration outcome from sciatic nerve repair with suture, fibrin glue or a combination of both techniques[7]. For this study, the data were not separated according to procedure, but rather were treated as independent data points, allowing analysis of correlations between nerve regeneration parameters obtained with the use of three different techniques. The whole surgical procedure was performed within a Faraday cage to reduce electromagnetic interference during electrophysiological evaluation.

All experiments were accomplished in two stages and were done in the right hind limb. In first stage, the rats were anesthetized with an intraperitoneal injection of diazepam (0.1 mL/animal) and ketamine chloridrate (50 mg/kg). All surgical procedures were carried out by the same surgeon, using a sterile microsurgical technique. The sciatic nerve was exposed through a gluteal muscle-splitting incision and was circumferentially dissected from the sciatic notch to its trifurcation. After a first electrophysiological evaluation, the nerve was transected midway between the sciatic notch and its division under 25x microscopic magnification (D.F. Vasconcelos, M900, D.F. Vasconcelos S.A., Brazil). Subsequently, three groups were randomly created consisting of 10 rats each, according to the adopted repair. In group A, the nerve ends were coapted with four 10-0 monofilament nylon epineurial sutures. In group B, the nerve ends were approximated and a fibrin-based tissue adhesive (Beriplast® Aventis, Marburg, Germany) was applied at two equidistant points to the epineurium of both proximal and distal stumps. In group C, repair was performed through a combination of the two techniques - a single 10-0 monofilament nylon epineurial suture and a subsequent fibrin glue application at a point diametrically opposed to the suture, following the same procedure as for group B. After nerve repair, the wound was closed in layers and the animals were caged separately, having free access to both dry chow and water.

In a second stage, at six months postoperatively, all rats were reexplored through the previous surgical incisions, after anesthesia with the same drugs described in the first surgery. The right sciatic nerve was exposed again and freed from surrounding tissues without disturbing the repair site. Subsequently, a new electrophysiological evaluation was performed, the nerve was ressected and the animals were killed with a lethal dose of pentobarbital injected intraperitoneally.

The evaluation of all parameters was performed in a blinded fashion so that the identity of each experimental group was not known while obtaining the parameters.

Walking-track analysis – At 12 weeks after nerve repair, the animals were submitted to walking-track analysis and measurement of the sciatic functional index (SFI) using a method similar to that described by De Medinaceli et al[8]. The trials were done in an 8.2x42 cm corridor darkened at one end and covered with a sheet of white paper. The rats' forepaws were dipped in black india ink and the animals were free to walk in the mentioned corridor. In most cases, a single walk by each animal was enough to obtain adequate prints on paper. From the analysis of the footprints of the operated and unaffected feet, the print length, toe spread and intermediary toe spread were obtained by hand measurement. The sciatic functional index was calculated as described by Bain et al.[9]. The evaluations of all animals were performed by a single investigator.

Electrophysiological evaluation – The electrophysiological studies were conducted before nerve section, during the primary operation, and after 6 months, during reoperation. The evaluation included measurements of the compound nerve action potential (NAP) and compound muscle action potential (MAP) parameters. After nerve exposure, two ground electrodes were installed - a monopolar straight needle electrode (26 G) and a helical electrode manufactured from 316L stainless steel wire. The straight needle was inserted within an adjacent muscle and the helical electrode was positioned surrounding the nerve. The configuration of the latter one increased the contact area.

Recordings were made on a two-channel electromyography system (Medtronic Keypoint portable, Skovlunde, Denmark), with the high-frequency filter set at five kilohertz and the low-frequency filter set at two hertz. For each one of the obtained potentials (NAP and MAP), the stimulus was a square electric pulse administered for 0.04 ms until the supramaximal stimulation amplitude was reached. The electrophysiological analysis was carried out with two bipolar hook electrodes for NAP measure, and with one (stimulating) bipolar hook electrode and a coaxial needle (recording electrode) for MAP measure. The bipolar electrodes were placed under the nerve; the MAP recording electrode was placed in the gastrocnemius muscle through percutaneous puncture in the distal third of the paw, ipsilaterally to the surgical procedure. Stimulation in NAP and MAP evaluation was always performed 2 and 3 cm, respectively, proximal to the distal electrode. After a 24-weeks interval from the first surgical procedure, a second electrophysiological evaluation was carried out by the same method described for the initial electrophysiological evaluation.

The following measurements were made: initial latency of NAP (LATN1), initial latency of MAP (LATM1), initial amplitude of NAP (AMPN1), initial amplitude of MAP (AMPM1), initial conduction velocity of NAP (CVN1), initial conduction velocity of MAP (CVM1), final latency of NAP (LATN2), final latency of MAP (LATM2), final amplitude of NAP (AMPN2), final amplitude of MAP (AMPM2), final conduction velocity of NAP (CVN2) and final conduction velocity of MAP (CVM2). For each evaluated potential, the ration between the initial and final measured values of amplitude and conduction velocity, expressed in percentage, was calculated (%AMPN, %AMPM, %CVN and %CVM).

Histomorphometric evaluation – Following the second electrophysiological evaluation during the second surgical procedure, the electrodes were removed and Karnovsky's fixative solution was instilled on the repaired sciatic nerve. After three minutes, the sciatic nerve of each animal was excised *en bloc* so that the specimen included segments proximal and distal to the repair site. Two 4-mm nerve specimens were harvested from each nerve 4 mm proximal and 4 mm distal to the repair site. These segments were fixed in Karnovsky's solution and postfixed with osmium tetroxide, dehydrated in a series of alcohol solutions and finally embedded in epoxy resin. Thin transverse sections (1 μm thick) were cut and stained with toluidine blue for examination under the light microscope. For each nerve segment, images were analyzed with a digital image analysis system linked to a histomorphometry software (Sigma Scan Pro 5.0, SPSS Inc., Chicago, U.S.A.).

Once the total number of fibers was counted in the segments proximal and distal to the repair site, five sampling fields were selected by a random sampling technique and the fiber perimeters were measured. From these data, the mean of fiber diameters was calculated in each segment. The total number of myelinated extrafascicular fibers in the distal segment was also counted.

Three indices, expressed as percentages, were determinate for all nerves harvested: the regeneration index (RI), calculated by dividing the total number of regenerated fibers in the segment distal to the repair site by the total number of regenerated fibers in the proximal segment; the extrafascicular regeneration index (ERI), obtained by dividing the total number of regenerated extrafascicular fibers in the segment distal to the repair site by the total number of regenerated fibers in the same segment; and the diameter change index (DCI), calculated by dividing the mean of fiber diameters in the segment distal to the repair site by the mean of fiber diameters in the proximal segment. The RI represented the percentage of axons that crossed the repair site.

Statistical analysis – Statistical analysis was performed using Bioestat 2.0 for Windows (Ayres M, Belém, Brazil). Pearson's correlation analysis was performed to establish the relationship between the 17 evaluated parameters of nerve regeneration (eight electrophysiological as well as eight morphometric parameters and one walking track parameter). A 0.01 significance level for statistical test was used. Given the number of animals (n=30) with complete data and the significance level used, a coefficient of correlation >0.5 was considered relevant.

RESULTS

By the end of the experiment, the rats had gained between 200 to 300 mg in weight on the average. No wound dehiscence occurred, but the animal loss rate was high. Eighty-six rats were necessary to obtain a final number of 30 animals. Ten rats died during anesthesia (3) or in the postoperative period (7), 17 animals presented muscle tendinous retraction, and 29 showed different kinds of lesions in the paws on the operated side secondary to autotomy. Retractions

Table 1. Data from electrophysiological parameters of nerve regeneration after repair of rat sciatic nerve with three methods.

CVN1 (m/s)	AMPN1	CVN2	AMPN2
86.96±29.97	1.19±0.59 mV	64.96±24.54 m/s	0.51±0.40 mV
%CVN	%AMPN	CVM1	AMPM1
79.75±31.55%	55.88±52.11%	19.79±3.06 m/s	4.97±2.20 mV
CVM2	AMPM2	%CVM	%AMPM
16.22±2.55 m/s	4.41±2.05 mV	83.76±17.73%	107.90±76.15%

Data are expressed as mean ±standard deviation. AMPM1, initial amplitude of compound muscle action potential; AMPM2, final amplitude of compound muscle action potential; AMPN1, initial amplitude of compound nerve action potential; AMPN2, final amplitude of compound nerve action potential; CVM1, initial conduction velocity of compound muscle action potential; CVM2, final conduction velocity of compound muscle action potential; CVN1, initial conduction velocity of compound nerve action potential; CVN2, final conduction velocity of compound nerve action potential; m/s: meters per second; mV, milivolts; %AMPM, ratio between initial and final amplitudes of compound muscle action potential; %AMPN, ratio between initial and final amplitudes of compound nerve action potential; %CVM, ratio between initial and final conduction velocities of compound muscle action potential; %CVN, ratio between initial and final conduction velocities of compound nerve action potential.

Table 2. Data from histomorphometric parameters of nerve regeneration after repair of rat sciatic nerve with three methods.

PF	DF	RI	PD
11981.33±1982.40	10723.77±1793.77	91.64±20.54%	10.83±3.54 μms
DD	DCI	EF	ERI
9.55±3.36 μms	88.10±10.03%	772.83±782.23	7.41±7.04%

Data are expressed as mean ±standard deviation. DCI, diameter change index; DD, distal fiber diameter; DF, total number of distal fibers; EF, distal extrafascicular fibers; ERI, extrafascicular fiber regeneration index; PD, proximal fiber diameter; PF, total number of proximal fibers; RI, regeneration index.

Table 3. Results of correlation between electrophysiological parameters and sciatic functional index.

	VCN2	AMPN2	%AMPN	%CVN	VCM2	AMPM2	%AMPM	%CVM	SFI
VCN2	1								
AMPN2	0.17	1							
%AMPN	0.11	0.79*	1						
%CVN	0.44	0.05	0.18	1					
VCM2	0.16	0.23	0.25	0.10	1				
AMPM2	0.39	0.45	0.39	0.01	0.14	1			
%AMPM	0.29	0.48	0.27	–0.003	0.05	0.36	1		
%CVM	0.30	0.09	0.38	0.06	0.63*	0.15	–0.14	1	
SFI	–0.34	0.34	0.39	–0.01	0.14	–0.14	–0.10	0.17	1

See Tables 1 and 2 for abbreviations. *p< 0.001; **p<0.01.

Table 4. Results of correlation between histomorphometric parameters and sciatic functional index.

	PF	DF	RI	PD	DD	DCI	EF	ERI	SFI
PF	1								
DF	0.06	1							
RI	–0.65*	0.71*	1						
PD	0.13	–0.17	–0.22	1					
DD	0.33	–0.23	–0.38	0.91*	1				
DCI	–0.51**	0.14	0.42	–0.03	–0.43	1			
EA	–0.46	0.05	0.38	0.02	–0.01	0.12	1		
ERI	–0.47	–0.18	0.22	0.06	0.06	0.05	0.97*	1	
SFI	–0.02	–0.10	–0.04	0.57**	0.50**	0.02	0.08	0.11	1

See Tables 1 and 2 for abbreviations. *p< 0.001; **p<0.01.

and lesions from autotomy prevented walking-track analysis, and those animals had to be sacrificed.

The correlations between 17 variables were evaluated. The mean and standard deviations of electrophysiological and morphometric parameters are presented in Table 1 and Table 2, respectively. In the three repair groups the SFI was –45.00±11.46.

Pearson's correlation analysis showed two kinds of relationship, one between the same category of parameters and other between different classes of regeneration assessment. In the electrophysiological evaluation, a positive correlation was identified between AMPN2 and %AMPN (r=0.79, p<0.001) and between CVM2 and %CVM (r=0.63, p<0.001). In the histomorphometric evaluation, the total number of fibers in the proximal segment correlated negatively with RI (r=–0.65, p<0.001) and with DCI (r=-–.51, p<0.01). On the other hand, the proximal fiber diameter was well correlated with distal fiber diameter (r=0.90, p<0.001). A strong correlation was also observed between the number of extrafascicular fibers in the distal segment and ERI (r=0.96, p<0.001). No correlations were established between electrophysiological and histomorphometric assessments. Regarding the functional evaluation, when SFI was compared with the other evaluation methods only two positive correlations were established - between the SFI and the proximal fiber diameter (r=0.56, p<0.01), and the SFI and the distal fiber diameter (Figure) (r= 0.50, p<0.01). The results of correlation between outcome measurements are presented in Tables 3 and 4.

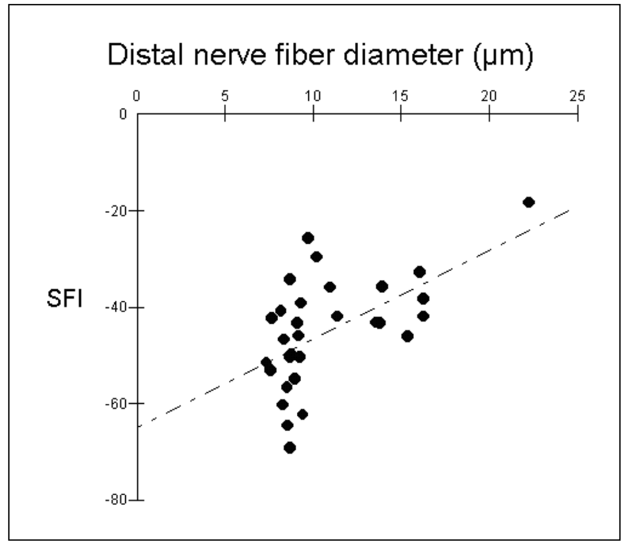

Figure. Graph showing the relationship between sciatic functional index and distal nerve fiber diameter. Correlation between sciatic functional index and distal nerve fiber diameter. There is a positive correlation between these parameters after three different repairs in sectioned rat sciatic nerve (r=0.50, p<0.01).

DISCUSSION

Peripheral nerve injuries are a commonly encountered clinical problem and often result in long-term functional deficits. Despite advances in microsurgical techniques, the functional outcome of peripheral nerve trauma is rarely satisfactory resulting in an extensive experimental investigation for the development of methods to improve regeneration. The rat sciatic nerve model has been largely used in these studies, and a variety of evaluation methods regarding regeneration has been described whose selection is critical for the researcher[3,10].

In the rat sciatic model, nerve morphometry, electrophysiological studies and measurement of functional recovery are the most popular methods to assess neural regeneration[6,11]. There are numerous tests to quantify the functional recovery by assessing toe, foot, ankle, and leg function, as well as gait and postural pattern[3]. One of the most commonly test, the sciatic functional index, provides a noninvasive and quantitative method to evaluate functional recovery of walking ability, the ultimate goal in the regeneration of injured rat sciatic nerve[2,6]. Nevertheless, one must keep in mind that sometimes this method cannot be used[2,9]. Chronic limb retractions, contractures and the occurrence of autotomy may impair the ability to use such method[1,2,10]. In our study, these complications affected 42 % of the rats, but can occur in up to 88% of the animals, making it unfeasible to use walking-track analysis in some studies[12-15]. The incidence of autotomy was found to be related to the type of injury, being more frequent in association with nerve section - the model used in our study - than with crush lesions. This fact should be considered in the choice of the evaluation method. Where investigation demands nerve section, autotomy can hinder completion of the study if it includes a walking-track analysis. Probably, the researcher will have more success with the gait analysis when working with crush lesions.

The selection of appropriate outcome measures to characterize the loss of function and recovery is critical for the success of a new experimental procedure involving nerve lesion and regeneration. A frequent question introduced by studies comparing the evaluation methods of peripheral nerve regeneration is whether it is possible to establish a correlation between functional evaluation and other more applied measures. In general, this correlation is seldom observed and the results of almost all literature on this matter corroborate our results[6,11,16-18]. An exception is the paper by Shen and Zhu[4], which reported the measurement of seven parameters in the electrophysiological and morphometric evaluations after nerve injury or sciatic nerve repair. The sciatic functional index presented a strongly positive correlation with all the evaluated parameters (r always >0.87).

Although the investigation of the correlations between nerve regeneration parameters is a well explored subject, we performed procedures with few previous utilization and knowledge. In the electrophysiological evaluation each animal was considered as your own control, allowing the obtainment of different indices after pre and postoperative evaluations. A similar way of investigation was used in the histomorphometric evaluation, i.e., the parameters measurements were performed in both proximal and distal segments allowing the calculation of indices which are rarely applied. Two kinds of significant correlation were observed in our results, one of them obtained within the same evaluation group, between electrophysiological parameters. This kind of correlation is easy to accept and have a different meaning from correlations observed between different types of regeneration assessments. In our study, only two weak correlations of different classes were obtained - between SFI and proximal fiber diameter (r= 0.50) and SFI and distal fiber diameter (r=0.57). This result was very similar to correlations obtained by Kanaya et al.[18] between fiber diameter, axon diameter, and myelin thickness and SFI. Another kind of correlation was verified by Dellon and Mackinnon[10], who found a strong positive correlation between CV of NAP and fiber diameter (r=0.92) and amplitude of compound action potential and number of nerve fibers (r=0.99)[6].

Most published studies, as well as ours, use nerve section as preferential lesion instead of a crush injury. In crush injury, the nerve regeneration is more effective due to the maintenance of basal lamina[19] and, therefore, after regeneration, this lesion enables a functional recovery in almost all cases. Few reports evaluated the correlation between regeneration evaluated parameters when different lesions (crush or section) were used. In two published articles the identified correlation did not depends on the type of lesion[20,21].

What is the best experimental method to evaluate peripheral nerve regeneration? According to several authors, walking track analysis is an overall functional assessment of peripheral nerve regeneration, with the correlation of this measure with other parameters being rarely observed[6,17,22,23]. So, shall we consider histomorphometric and electrophysiological evaluations to be inadequate in regeneration assessment after peripheral nerve repair? Actually, many authors accept that these methods evaluate different stages of regeneration and, consequently, cannot be compared[17]. Histomorphometry would be effective to quantify the modifications in the number and diameter of the fibers after repair, while electrophysiology evaluate a subpopulation of regenerated fibers which are electrically more effective. However, if we consider functional quality, maybe only some of the regenerated fibers are viable; moreover, the regenerating axons may present a misdirected growth leading to an aberrant muscle reinnervation[10,24] and the presence of polyneuronally innervated muscle fibers may reduce the efficiency of peripheral nerve regeneration[25].

Based on the results of the present and published studies, the most adequate question should be: which stage of nerve regeneration do we wish to study? For example, if the study aims at evaluating a new suture technique after nerve division, with an obstacle in the repair area, histomorphometry will be an adequate procedure. In such case, this assessment could be complemented with electrophysiological analysis, with measurement of pulse transmission at the repair site, which would be detectable by NAP evaluation, and assessment of nerve integrity to the level of muscular fibers by compound muscle action potential measurement. On the other hand, if the nerve section is not considered, the functional assessment should be the main evaluation method, replacing the electrophysiological evaluation at late stages of regeneration.

In conclusion, we have shown in our experimental setting that there are no significant correlations between the functional assessment of peripheral nerve regeneration and the morphometric/electrophysiological evaluations. Additionally, autotomy and chronic limb retraction can make it unfeasible the walking-track analysis, when nerve section is the standard procedure in a study aimed at evaluating peripheral nerve repair.

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