



The influence of reinnervation on the results of peripheral nerve repair after injuries

Original Study

Krzysztof Suszyński¹, Natalia Białoń^{*1}, Wiesław Marcol², Dariusz Górka¹, Mikołaj Górka³

¹Department of Sports Medicine and Physiology of Physical Exercise Faculty of Health Sciences in Katowice Medical University of Silesia in Katowice Poland

²Chair and Department of Physiology Faculty of Medical Sciences in Katowice Medical University of Silesia in Katowice Poland

³Center of Experimental Medicine of the Medical University of Silesia in Katowice Poland

Received 14 October, 2022, Accepted 21 March, 2023

Abstract

Introduction. Research on the possibility of increasing the effects of after-injury reconstruction of peripheral nerves conducted in the Department of Physiology at SUM resulted in the development of a new method of reconstruction after peripheral nerve injuries. In this new method, we used 7-day predegenerated *in situ* sural nerve grafts. In clinical assessment, we concluded that recovery in motor, sensory and vegetative function after peripheral nerve injury treatment is better with the use of predegenerated grafts. The latent efficacy of reconstruction was measured months or years after reconstruction. In that amount of time, denervated synaptic sites in muscles can be reinnervated by nearby healthy non-injured nerves. It could increase motor, sensory, or vegetative function, irrespective of the effects of surgical treatment. We decided to investigate whether the circumstances may influence the latent efficiency of the new method of reconstruction.

Materials and Methods. Experiments were carried out on 32 patients in The Department of Neurosurgery Medical University of Silesia. Twenty patients were operated on with a predegenerated (P) implant, and 12 patients operated in the traditional method (T). As a result, 25% of patients' reinnervation from healthy nearby nerves in the area supplied by reconstructed nerves was present. In group P, reinnervation appeared in 7 of 20 patients (35%) and in group T, in 1 from 12 (8.33%) cases.

Results. Results of the examinations were counted statistically in both groups.

Conclusion. Reinnervation from nearby healthy non-injured nerves positively influences the results of human peripheral nerve reconstruction.

Keywords

reinnervation • predegeneration • peripheral nerve • nerve reconstruction

1. Introduction

Nerve damage triggers complex molecular processes within the cell that are necessary for the process of axon regeneration, and thus for restoration of functional potential in patients with structural changes in peripheral nerves [1]. Advances in neurosurgery using modern microsurgical techniques have resulted in more effective regeneration of degenerated nerves [2]. Nevertheless, at the functional level, these results have still been unsatisfactory [3]. When the axon has undergone processes of impingement, crushing, or stretching, a process of Wallerian degeneration occurs [4]. During the process of nerve reconstruction, Schwann cells are involved in the remyelination process, but the myelin sheath that is formed is much thinner than before the damage and thus results in changes in the conduction of nerve impulses [5]. At the molecular level, markers indicative of the nerve reconstruction mechanism include transcription factors such as MYC [6], HIF1α [7], CREB1 [8,9], SOX11 [10–14], TP53 [15,16], and SRF48 CZY XBP1 [17,18]. Their exact mechanisms of action are still unknown, and the list of possible candidates for transcription factors involved in repair processes is constantly being updated with new proteins. Hence,

there is an ongoing need to search for methods to gain a large-scale understanding of the factors involved in the regeneration of nerves undergoing degeneration [1]. Research by Marcol et al. (2003) has demonstrated the importance of predegenerated nerves in the mechanism of enhancing morphological features indicative of regenerative processes within peripheral nerves in rats [19].

This research on neuritis regeneration has been conducted in Physiology Department, Medical University of Silesia. Regeneration in adult mammals shows significant differences when a microsomal fraction of predegenerated nerves was used (the ischial nerve of adult rats was cut seven days earlier and left *in situ* until collection). Based on this research, predegenerated nerve grafts were examined as a method of nerve-injury surgery in the Neurosurgery Department of the Medical University of Silesia. This new method was established in patients with injuries to their radial, ulnar, or medial nerves. The sural nerve (graft) was cut seven days before reconstruction. Its distal section was marked and left *in situ* until the final reconstruction procedure. Microsurgical reconstruction of the injured antebachial nerve was performed after seven days. The distal

* E-mail: d201080@365.sum.edu.pl



and proximal stumps of the reconstructed nerve were localized and refreshed; epineurium was cut to show individual fascicles. The predegenerated sural nerve was collected, and two or three nerve cables were implanted and provided with perineural suture (10.0 monofilat) without tension.

Clinical achievement of regeneration may be diminished in the event of a mass innervation phenomenon. This situation can occur if regenerating axons reach an improper target (for example, if growing proximal stump axons reach improper runners, Schwann cell columns among Hanke-Büngner strands outgrowing distal stump). The muscle, together with the motor nerves that form it, undergoes cyclic changes leading successively to denervation and reinnervation. Consequently, a transient disconnection of the motoneuron from the innervating muscle is observed. If the motoneuron remains intact, it can either interact with the muscle again or be additionally innervated by the outgrowth of a lateral branch of a neighboring motor neuron axon [20–23]. The reinnervation process in muscular fibers results in an increase of amplitude of the motor unit, as well as in its elongation [24]. The phenomenon in which lateral branches of an undamaged nerve form synaptic connections with uninjured tissue is called “collateral sprouting” [25,26]. The stimulus that promotes this process is Wallerian degeneration, as well as an increase in the expression of those genes whose protein products are involved in the regeneration of the damaged nerve [27,28]. The aim of this work is to investigate whether a reinnervation process with nearby seated, non-injured nerves can influence latent efficiency of peripheral nerves’ predegenerated reconstruction.

2. Materials and methods

Thirty-two patients aged 16–65 (mean 39 ± 35 , 8 years), female and male (4 and 28, respectively), were operated on in The Department of Neurosurgery at the Medical University of Silesia in Katowice. A period of two years following the operation was chosen as the time of final clinical assessment, due to axonal regrowth velocity and muscle mass rebuild time. In 19 patients, reconstruction of the ulnar nerve was performed. The median nerve was repaired in 11 cases and the radial nerve in 2 cases. The length of the gap varied from 2 to 6 cm. In this group, 62.5% of patients were right-handed, but only 37.5% of patients were injured in their dominant hand. In 20 patients, reconstruction of injured nerves was made with the 7-day-predegenerated sural nerve graft (group P). In 12 other patients, traditional autological grafting was performed (group T). The time from injury to reconstruction was between a few weeks and a few years. Axonal regeneration after reconstruction occurred for as long as two years. This is the reason for latent efficiency of reconstruction, which could be finally estimated after a few years. In this period, denervated synaptic sites in muscles can be reinnervated by nearby healthy non-injured nerves, increasing motor, sensor, or vegetative function irrespective of the effects of surgical procedures.

This is the reason for our decision to investigate whether reinnervation with nearby seated, non-injured nerves can influence latent efficiency of a new method of peripheral nerve reconstruction. Additionally, we divided our group of patients (regardless of surgical treatment) into two groups:

- R– with reinnervation (n=10),
- NR– without reinnervation (n=22).

2.1. Hand muscle strength

For evaluation of muscle strength, dynamometric measurement method using a Baseline hand dynamometer was employed. Muscle strength of the impaired hand was expressed as a percentage of the healthy hand’s strength (Hand Muscle Strength Index – HMSI).

2.2. Hand volume

Volume of the hand up to distal-most wrist crease was measured, and volume of the impaired hand was expressed as percentage of the healthy hand’s volume (Hand Volume Index – HVI).

2.3. Motor function and Sensory function

For evaluation of motor function and sensory recovery, British Medical Research Council (MRC) scales were used.

MEDICAL RESEARCH COUNCIL (MRC) GRADING FOR MOTOR FUNCTION:

- M0 – no contraction, paralyzed
- M1 – flicker of contraction
- M2 – contraction with gravity eliminated
- M3 – contraction against gravity
- M4 – contraction against resistance
- M5 – normal power

MEDICAL RESEARCH COUNCIL (MRC) GRADING FOR SENSORY FUNCTION:

- S0 – no sensation
- S1 – pain sensation
- S2 – pain and touch sensation
- S3 – pain and touch with no over-reaction
- S3+ – some two-point discrimination
- S4 – normal sensation

2.4. Vegetative changes

For evaluation of autonomic changes in the impaired hand, a special scale was created. The following properties were taken into consideration: sweating disorders, color, temperature, and humidity of the skin in area supplied by the reconstructed nerve. A grade of 1 meant extensive vegetative changes, 2 signified noticeable changes, and 3 meant no noticeable changes.

The electrophysiological assessment of the peripheral nerve’s function after using the surgical treatment was made

with electroneurography (ENG) tests. Nerve conduction velocity testing (NCV) is used to evaluate damage or disease in peripheral nerves. Examinations were performed in the Department of Neurosurgery of the Central Clinical Hospital Medical University of Silesia in Katowice. In the injured arm, standard motor and sensory nerve conduction tests of the median and ulnar nerves were performed (apparatus; Viking 4D, electrodes; Nicolet Biomedical, surface electrode). For the median nerve, motor potentials were recorded from the abductor pollicis brevis muscle, with stimulation at the wrist and elbow crease. Sensory responses were recorded at the wrist with stimulation of one nerve in the thumb, index, long and ring fingers, and the radial part of the palm, respectively. Ulnar nerve motor responses were recorded from the abductor digiti minimi muscle with stimulation at the wrist, below and above the elbow. Sensory potentials were recorded at the wrist after stimulation of one nerve per ring and little fingers and the ulnar part of the palm.

The examination consisted of two main parts: motor MNCS and sensory SNCS recording. The evaluation of the conducted assessment was based on analysis of the conduction velocity, onset latency and amplitude of action potential.

The results were presented as:

- (1) Expansion of conduction.
- (2) Reference of the relative value to exemplar value for the given type of nerve.
- (3) The assessment of conduction parameters according to 4-grade scale: grade 1 - the absence (or the trace) of the answer; grade 2 - clear answer to abnormal parameters; grade 3 - the clear answer from similar parameters to regular; and grade 4 - the (clear) answer to regular parameters.
- (4) The presentation of results as the average values of conduction parameters.

Quantitative data are presented as mean + Standard Error. All data were statistically analyzed using regression testing and one-way analysis of variance followed by Tukey for continuous values, and the Mann-Whitney U test for ordinal values. Differences were considered statistically significant for $p \leq 0.05$.

3. Results

Collateral reinnervation from undamaged, healthy nerve fibers estimated on the basis of ENG examination was observed in 25% of patients operated in our clinic. A greater (but not statistically significant) rate (35%) of reinnervation was found in patients who underwent the implantation of predegenerated grafts. In this group ($n=20$), reinnervation from nearby-sited nerves was found in seven patients. In the group of patients who underwent the traditional cable implant (without predegeneration), this phenomenon was only found in one patient (8.33%).

Higher grades on the MRC scale ($p=0.84$) were observed in R group ($p=0.20$; statistically not significant). Results obtained on

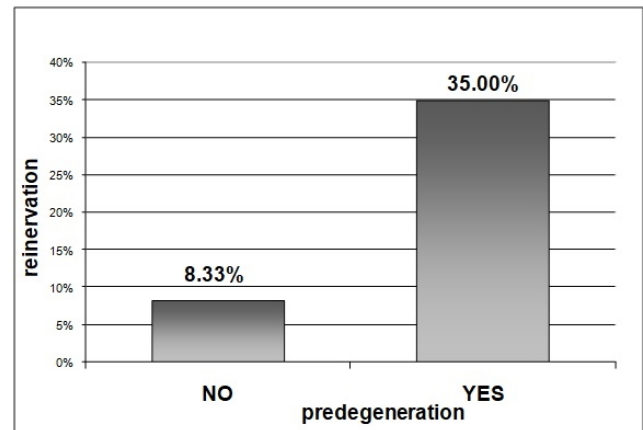


Figure 1. Reinnervation and predegeneration

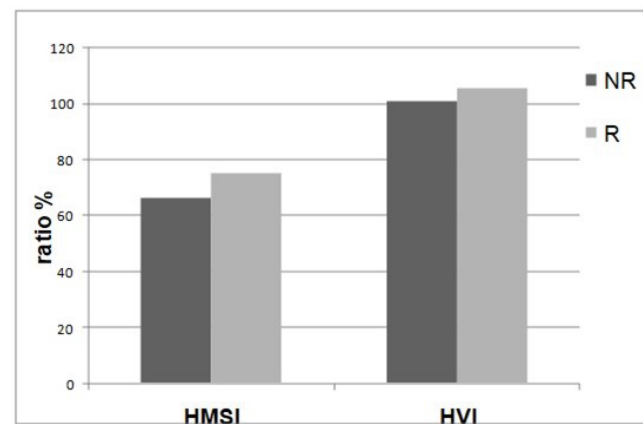


Figure 2. Hand muscle strenght indeks and Hand volume indeks

the HMSI scale and HVI scale show slightly better but statistically not significant (Mann-Whitney U test) outcomes for patients in whom reinnervation was observed.

The age of the patient was found to be a statistically significant ($p=0.03$) factor affecting the motor function. Older patients scored worse in movement range.

Electroneurographical examination of motor fibers confirms better outcomes in the R group patients. Reference of the relative value of amplitude of motor conduction evoked potential (PNR) to exemplar value for the given type of nerve analysis shows the positive impact of collateral sprouting on the amplitude of evoked potential.

In the R group, amplitude values are more similar to due value ($p=0.54$). These results are in accordance with the fact that more of the patients in group R achieved the fourth grade of electrophysiological improvement ($p=0.04$). The mean value of amplitude in PNR examination was higher in group R for both the ulnar and median nerve (4.9 mV and 6.9 mV, respectively) in comparison with the NR group (3.11 mV and 3.15 mV, respectively).

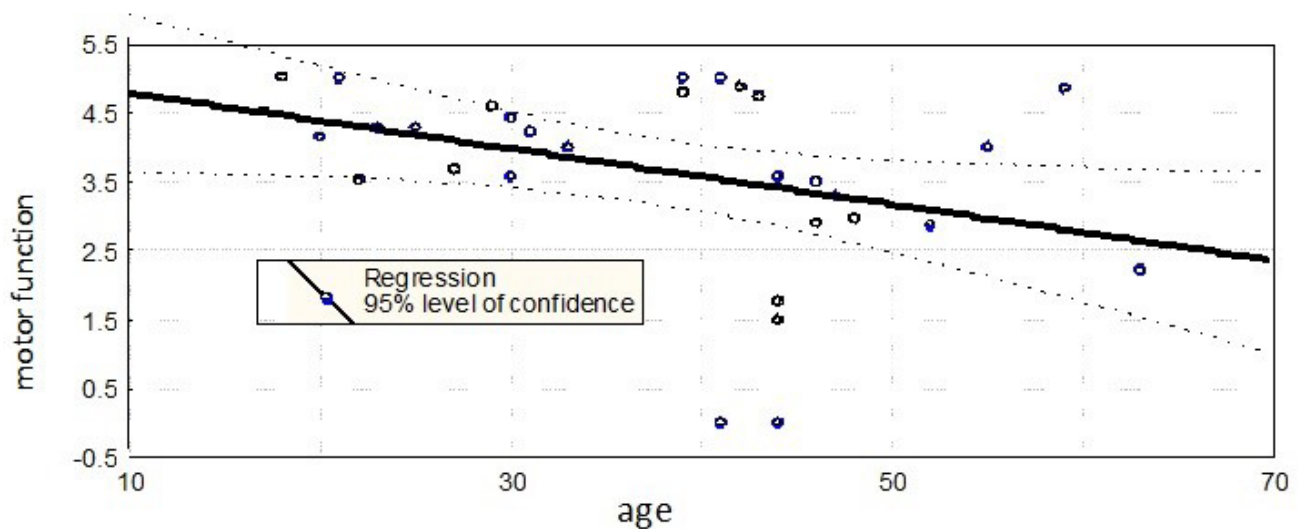


Figure 3. The regress analysis motor function and age

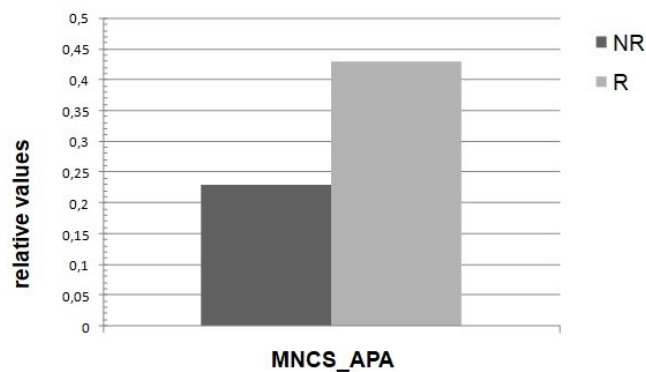


Figure 4. Relative values of action potential amplitude of motor nerve conduction study (MNCS_APA)

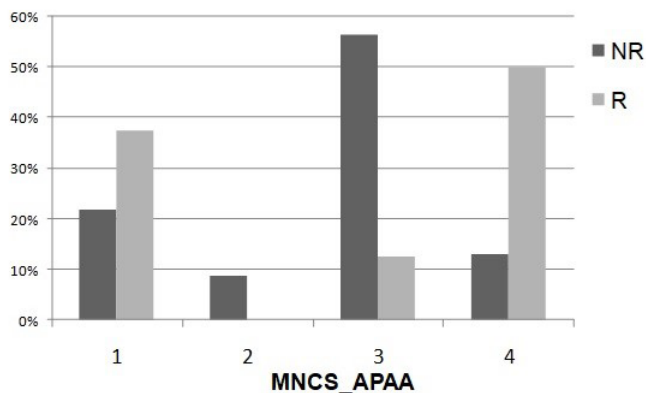


Figure 5. Mean value of amplitude according to 4-grade scale

Dynamometric measurements show that relative value of muscle strength of the impaired hand, in comparison with the other hand in patients with dominant hand injury, was higher in group R. The volume of the impaired hand compared to the healthy hand volume was greater in patients in whom reinnervation had developed. ($p=0.01$; Mann-Whitney U test)

Unfortunately, the number of reinnervation cases in which the subdominant hand was injured ($n=2$) was too small to obtain relevant conclusions. Vegetative disorders appeared less frequently in the group with reinnervation; almost half of the patients in the R group did not show any autonomic disorders.

4. Discussion

The above analysis shows that reinnervation positively affects all measured parameters. We emphasize the fact that reinnervation from nearby seated, non-injured nerves occurred only in the group with predegenerated grafts. This study shows statistically significant negative influence of age of patients on the motor and sensory function. ENG examination shows better results achieved in patients from the R group. The NCV examination consisted of two main parts: motor NCS and sensory NCS. The evaluation of the conductivity was done on the basis of conduction velocity, onset latency and amplitude of action potential. Patients in the R group achieved better results in both motor and sensory assessment after two years of observation. The age of the patient and the type of injury (dominant hand) had significant impact on the return of injured nerve function. Furthermore, reinnervation showed statistically significant influence on the amplitude of action potential in the motor nerve conducting test, which emphasizes its influence on faster strength return.

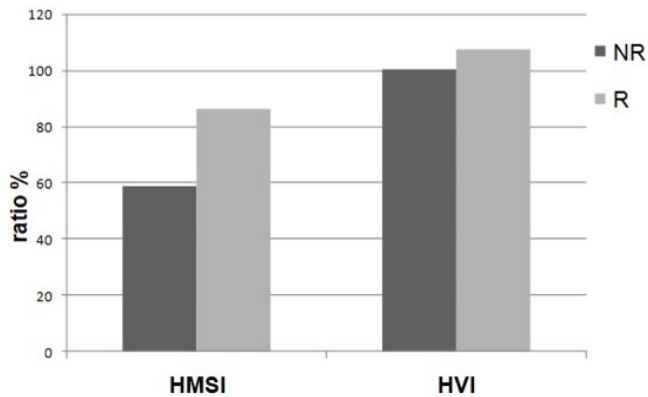


Figure 6. Hand muscle strength index (HMSI) and Hand volume index (HVI) in group of patients with injured dominant hand

Over the last 30 years, enormous progress in peripheral nerve surgery has occurred. Despite the wide spectrum of scientific research conducted in different medical centers, there is still no strategy established as most successful in the reconstruction of injured nerves.

Using animal models, research continues to develop effective methods to improve peripheral nerve regeneration. According to a review of the literature, brief low-frequency electrical stimulation of the nerve proximal to the site of injury, or the use of autologous grafts or stem cells using neurotrophic factors, may represent great promise as a strategy for the reconstruction of damaged nerves [29–34]. Different conceptions of contemporary neurophysiologic investigation conducted on animals are only occasionally implemented in people.

It is worth noting the close relationship between the cortex and peripheral nerves. It is confirmed that cortical plasticity can be important and is an integral element for improving functional recovery after peripheral nerve damage [35–37].

Still, there are possibilities of using individually designed targeted rehabilitation. Modern methods that enable faster regeneration of damaged axons, as well as efficient sensory and movement reeducation, should be also included. Many sophisticated health programs are used for this purpose, and many developed clinical rehabilitation programs demand interdisciplinary rehabilitation teams. There is still little work on modern rehabilitation programs in combination with modern surgical techniques. However, there are emerging opinions in a few papers that a modern combination of surgical treatment and rehabilitation programs, with the use of rehabilitation robotics, could be an innovative way forward [38–41].

Genetic modification or microprocessor implantation can also contribute to the efficiency of nerve regeneration [42,43]. Minimal differences between the dominant and the non-dominant hand in the range of tested muscle strength in patients with traditional non-predegenerated, autologous grafts were observed by Thumble et al. [44]. However, clinical investigation conducted in our clinic proved that the HMSI in patients with injured dominant

hand was higher in patients in the R group. Furthermore, we found a significantly higher HVI in the group with reinnervation.

Too long of a period from the time of injury to time of final reconstruction of the nerve negatively affects the eventual outcome of final clinical assessment; this observation correlates with results presented by Jaremczyk [45]. Better results in peripheral nerve reconstruction were demonstrated more frequently in younger people than in patients in advanced age [46–48]. Investigation of the length of the lesion and achievement of recovery showed that a longer gap results in less efficiency of cutaneous nerve implants [46,49]. The findings of an investigation of the efficiency of predegenerated implants in animals published in 2006 [50] are in accordance with results obtained in our study. Additionally, we took into consideration collateral sprouting as a factor of final results.

5. Conclusions

1. Due to the shorter time before beginning the regeneration, predegeneration of autologous implants results in better quantitative and qualitative functional improvement.
2. A new method with the autologous, predegenerated sural nerve implant offers better results than use of a fresh implant in reconstruction of a peripheral nerve injury.
3. Predegeneration improves axonal regeneration, which leads to faster electrophysiological function improvement.
4. Collateral sprouting protects denervated muscle fibers.
5. Innervation of area anatomically characteristic of reconstructed nerve was observed in NCV examination both before and after surgery. We bind this phenomenon with a long period of time between injury and surgery, as well as with the neurotrophic features of a predegenerated implant.

Abbreviations

ENG – Electroneurography

HMSI – Hand Muscle Strength Index

HVI – Hand Volume Index

MNCS_APA – Motor Nerve Conduction Study - Action Potential Amplitude

MNCS_APAA – Motor Nerve Conduction Study - Action Potential Amplitude Assessment

NCV – Nerve Conduction Velocity

Acknowledgments

This paper was financially supported by the School of Medicine in Katowice.

Authors' contribution

Research concept and design: Krzysztof Suszyński, Wiesław Marcol, Dariusz Górka.

Supervising the project: Krzysztof Suszyński.

Carrying out the experiments: Krzysztof Suszyński, Wiesław Marcol, Dariusz Górka.

Acquisition of data: Krzysztof Suszyński, Dariusz Górka.
 Data analysis and interpretation: Natalia Białoń, Mikołaj Górka.
 Writing - Original Draft Preparation: Natalia Białoń, Mikołaj Górka.
 Writing - Review and Editing: Krzysztof Suszyński, Mikołaj Górka.
 Visualization: Natalia Białoń.
 Literature review: Natalia Białoń.
 Final proofreading and approval of the version for publication: Krzysztof Suszyński, Dariusz Górka.
 Funding Acquisition: Dariusz Górka.

ORCID

Krzysztof Suszyński <https://orcid.org/0000-0001-5694-1377>
 Natalia Białoń <https://orcid.org/0000-0001-7837-9370>
 Dariusz Górka <https://orcid.org/0000-0001-9727-4486>
 Wiesław Marcol <https://orcid.org/0000-0002-8914-7273>
 Mikołaj Górka <https://orcid.org/0000-0002-4852-3519>

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