"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

RESEARCH DIRECTIONS IN NERVE REGENERATION

PhD THESIS SUMMARY

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2025

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Introduction

Microsurgery represents the most complex and challenging branch from the Plastic, Aesthetic, and Reconstructive Microsurgery specialty. To excel in this fascinating field, a systematic development of surgical skills is required—starting with basic surgical techniques, followed by the refinement of precision techniques, and only then the training and improvement of microsurgical techniques. Developing and perfecting skills in this field demands sustained and continuous effort, with countless hours of practice, patience and composure. Mastering the microsurgical abilities opens up new horizons regarding what can be achieved in terms of surgical techniques and provides the foundation for performing extremely complex surgical interventions, enabling us to offer our patients the best possible solutions to their problems.

The main areas of interest in this surgical branch are vascular microsurgery and peripheral nerve microsurgery. While in vascular microsurgery an experienced surgeon can achieve relatively predictable outcomes, in the case of peripheral nerve injuries, the functional recovery results are less predictable and depend on a multitude of factors.

Peripheral nerve injuries are frequently encountered and represent a challenge in microsurgery due to complications associated with nerve repair (such as neuroma formation, sensory and motor deficits) and the socioeconomic burden that come with it [1-2].

Direct coaptation of nerve ends using epineural microsutures remains the standard surgical approach for severe injuries such as axonotmesis and neurotmesis [3]. When there is a gap between the nerve ends that creates excessive tension for direct epineural coaptation, alternative solutions are needed to connect the remaining nerve stumps and provide support for axonal regeneration. Human autografts are preferred, as evidence shows that autografting is superior to nerve conduits in long defects (greater than 3 cm), proximal injuries, and main nerves [3–4].

However, the use of autografts comes with several disadvantages, including limited availability, the need for another surgical site, and donor site morbidity. Due to these drawbacks, alternative solutions are necessary to address nerve gaps. Therefore, most studies have focused on the development of nerve guidance conduits used to support axonal growth and the addition of regenerative therapies to improve functional outcomes [5].

I chose this topic precisely because of the complexity of nerve injuries, the challenges they pose regarding functional recovery, and the impact they have on the daily lives of patients, as well as due to my passion for this microsurgical field.

Peripheral Nerve Injuries

Peripheral nerve injuries represent a significant pathology that disrupts communication between the central nervous system and the rest of the body, interfering with sensory, motor, and autonomic functions. These injuries can be caused by direct trauma, prolonged compression, ischemia, inflammatory processes, or systemic diseases such as diabetes mellitus [6,7]. The classification of these injuries is essential for assessing severity, treatment indications and predicting the outcome. The classifications proposed by Seddon and Sunderland are most commonly used, providing a grading scale ranging from temporary blockages (neurapraxia) to complete transections of the nerve (neurotmesis) [6,8].

From a pathophysiological perspective, any injury initiates a complex process of degeneration and regeneration. In particular, Wallerian degeneration—a process in which the distal end of the injured axon deteriorates—plays a central role. Schwann cells, essential components of the peripheral nerve, dedifferentiate, dispose of the cellular debris and form Büngner bands—structures that guide regenerating axons toward their targets [9,10]. Additionally, macrophages, laminins, integrins, and neurotrophic factors such as NGF and GDNF contribute to maintaining a pro-regenerative microenvironment [11,12].

Therapeutic Management

The therapeutic strategy is determined by the type and severity of the injury. In cases where the nerve ends are close and well-vascularized, direct end-to-end repair is the preferred method [13]. For more extensive injuries, autologous nerve grafts are necessary and are considered the gold standard, though they carry some disadvantages such as morbidity at the donor site and limited availability [14].

For larger defects, vascularized grafts may offer a superior solution, particularly in poorly perfused areas or in complex injuries [15]. In cases where neither direct repair nor grafting is feasible, nerve transfers may be applied. These involve rerouting a healthy donor nerve to reinnervate an affected area, with partial sacrifice of the donor nerve's function. Another technique, end-to-side neurorrhaphy, has been reintroduced recently but remains controversial in terms of its motor efficacy [16].

In selected cases, particularly when donor tissue is lacking, nerve allografts from human donors can be used, requiring a reduced form of temporary immunosuppression [16]. New research emphasizes the fact that nerves have low immunogenicity, allowing for gradual replacement of donor cells by host cells [17].

Another important direction in the treatment of nerve injuries is the use of nerve guidance conduits—tubes made from biological or synthetic materials that serve as scaffolds for axonal regeneration. These are useful in defects of up to 3 cm and can be made of collagen, polyglycolic acid, polycaprolactone, chitosan, or hybrid materials [18].

Research Directions in Nerve Regeneration

Advancements in tissue engineering and biotechnology have made major contributions to nerve regeneration. 3D printing allows for the fabrication of personalized nerve conduits adapted to patient anatomy, with complex geometries and multilayer structures [19].

Nanotechnology, through the use of graphene and carbon nanotubes, provides structural support and electrical conductivity necessary for axonal regeneration, although biocompatibility challenges persist [20]. Furthermore, research is focused on growth factors (NGF, BDNF, GDNF), delivered locally through biomaterials, hydrogels, or genetic vectors, including CRISPRa, to stimulate regeneration [21,22].

Mesenchymal stem cells, particularly those derived from adipose tissue, have shown great promise due to their ability to differentiate into Schwann-like cells, secrete neurotrophic factors and modulate inflammation. Exosomes from these cells enhance regenerative effects and are used in combination with biomaterials for controlled release [14,23].

Pharmacological interventions such as tacrolimus, melatonin, vitamin B12, lipoic acid, erythropoietin, or curcumin have demonstrated positive effects on nerve regeneration in preclinical studies by reducing oxidative stress and inflammation and by stimulating axonogenesis and myelination [24,25].

Finally, electrical stimulation represents an important adjuvant therapy, positively influencing gene expression involved in regeneration, promoting the secretion of neurotrophic factors, and facilitating axonal reorganization [26].

Purpose and Objectives of the Study

Although significant progress has been made in the field of microsurgery and peripheral nerve surgery, both in terms of infrastructure and surgical techniques, functional outcomes are still unsatisfactory. For this reason, research in the field of peripheral nerves remains highly relevant and necessary to improve functional results.

This paper began with a thorough review of the specialized literature to establish the current state of knowledge and to formulate pertinent working hypotheses aimed at improving clinical practice. Subsequently, I decided to continue the research in two directions. The clinical component involved the implementation of retrospective observational clinical studies, through which we could obtain an overview of the epidemiological data of patients presenting with peripheral nerve injuries of the upper limb, and formulate a series of observations that could guide us toward more effective prevention strategies and optimal treatment to achieve satisfactory functional outcomes.

The second direction undertaken in this paper consisted of a series of experimental studies on animal models, focusing on two aspects. On one hand, I analyzed the effectiveness of an aortic conduit in guiding axonal regeneration after creating a nerve defect, compared with the gold standard represented by autografts, and evaluated the outcomes after the addition of adjuvant regenerative therapies — in this case, nanofat. On the other hand, I laid the foundation for a preliminary study aimed at testing a collagen conduit, developed in collaboration with the National Institute for Research and Development in Textiles and Leather, a conduit designed to be economically sustainable within our healthcare system.

The objectives of the clinical studies were to analyze the distribution of nerve injuries within the population, to understand the mechanisms behind the occurrence of nerve injuries in our population in order to enable more effective prevention and reduce their incidence, to evaluate the surgical outcomes of nerve transfers in patients with brachial plexus injuries, and to compare outcomes between total brachial plexus injuries and upper brachial plexus injuries, between obstetrical and adult populations with brachial plexus injuries, as well as to compare our results with those available in the literature.

In the first experimental study, I aimed to compare, using an animal model, an aortic conduit filled with striated muscle fibers with autografts — the current gold standard in the repair of nerve defects — and assess the improvement in outcomes after the addition of regenerative therapies. The goal of the second experimental study was to test a therapeutic protocol involving a collagen conduit created in our country at low cost. The need for such studies arises from the fact that, although autografts provide satisfactory outcomes, there is room for improvement. Furthermore, the use of autografts is limited due to the availability of donor nerves, the requirement for a second surgical site for nerve harvesting, and the creation of sensory deficits at the donor site.

Materials and Methods

As part of the doctoral studies, I set the following research directions, detailed in Figure 1.

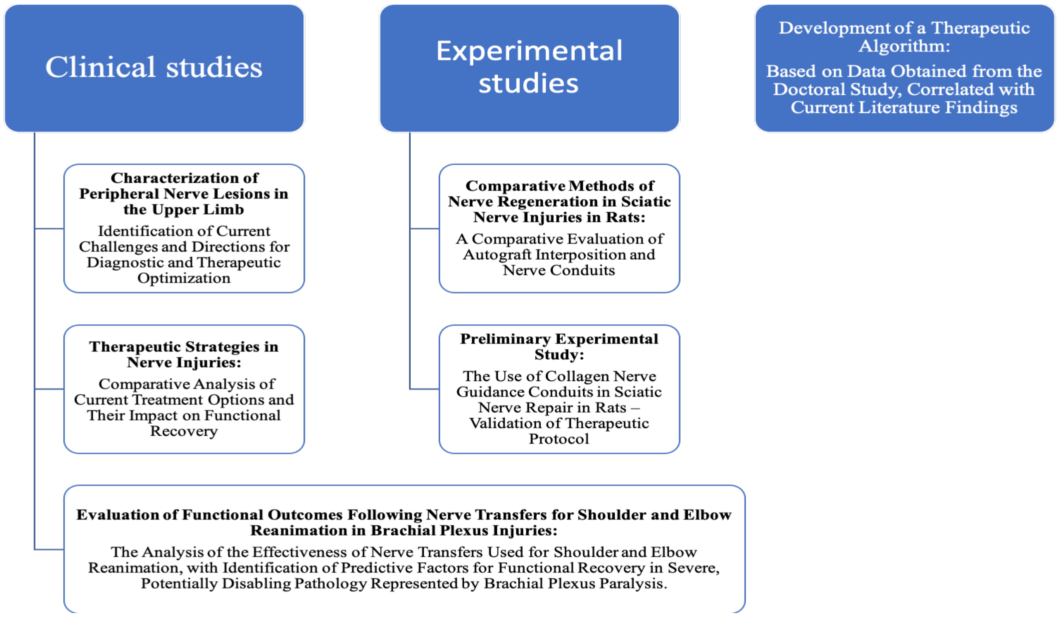

Figure 1. Study directions within the doctoral project

I designed 3 retrospective clinical studies analyzing the distribution and therapeutic principles in peripheral nerve injuries of the upper limb, and 2 experimental studies on animal models. Both the clinical and experimental studies were conducted mainly at the Emergency Clinical Hospital of Bucharest, except for the analysis of brachial plexus injuries, which was carried out multicentrically. The details of the 3 clinical studies are presented in Table 1.

Table 1. Conducted clinical studies

Title	Analyzed Period	Study Type
Characterization of Peripheral Nerve Injuries in the Upper Limb	January 2015 – December 2023	Retrospective study
Therapeutic strategies for nerve injuries: current findings and future perspectives	January 2017 – December 2019	Retrospective study
Functional outcomes following nerve transfers for shoulder and elbow reanimation in brachial plexus injuries	January 2015 – December 2024	Retrospective study

The first experimental study was conducted on 15 Wistar rats and consisted of creating a 0.5 cm nerve defect at the level of the right sciatic nerve and repairing it using various surgical techniques. The 15 rats were divided into 3 groups, 5 rats per group, as follows:

- Group 1 – nerve autograft (control group)
- Group 2 – interposition of a nerve conduit created from aorta and filled with striated muscle fragment
- Group 3 – interposition of a nerve conduit created from aorta and filled with striated muscle fragment and processed fat

The second experimental study was conducted on 10 Wistar rats and consisted of creating a 0.5 cm nerve defect at the level of the right sciatic nerve and repairing it through the interposition of a collagen nerve conduit filled with a striated muscle fragment, aimed at validating a therapeutic protocol involving a conduit developed locally, at reduced cost.

The materials and methods for each individual study will be detailed in the following chapters.

Clinical Study I: Characterization of Peripheral Nerve Injuries in the Upper Limb

We conducted a retrospective epidemiological study involving a cohort of 611 patients admitted to the Plastic Surgery and Reconstructive Microsurgery Clinic of the Bucharest Emergency Clinical Hospital with traumatic peripheral nerve injuries between January 1, 2015, and December 31, 2023. The inclusion criteria were patients admitted with traumatic peripheral nerve injuries in the upper limb. The exclusion criteria: nerve injuries of other etiologies, such as tumor-related pathologies or compression injuries, as well as injuries of the proper digital collateral nerves.

The study collected the following data: patients age, gender, mechanism of injury, affected nerve, anatomical location of the nerve injury, associated injured structures, duration of hospitalization, surgical technique used, and the calendar period in which the trauma occurred.

We analyzed the incidence of traumatic peripheral nerve injuries in relation to the total number of admissions at the country's largest trauma center, the Bucharest Emergency Clinical Hospital. The study assessed the distribution of patients by gender and age group, the distribution of nerve injuries by anatomical location, the percentage of injuries for each nerve type, the incidence of multiple nerve injuries, and the presence of associated damaged structures. The mechanism of injury was examined and correlated with patient gender. The calendar period of trauma events was analyzed and correlated with injury mechanisms.

Our study included a total of 611 patients admitted to the plastic surgery department of the Bucharest Emergency Clinical Hospital with upper limb peripheral nerve injuries, totaling 776 injured nerves. The overall incidence of peripheral nerve injuries in the studied population was 0.24% relative to the total number of hospital admissions. The annual incidence ranged from 0.16% to 0.34%. Considering only admissions to the plastic surgery department, the overall incidence was 3.08%, ranging from 2.1% to 5.45%.

Regarding gender distribution, there was a clear male predominance: 523 of the 611 patients were male (85.6%), and 88 were female.

The patients ages ranged from 3 to 87 years, with a mean of 43.28 ± 15.63 years. Most patients were in the 40–49 age group (137 patients – 22.42%) and the 30–39 age group (134 patients – 21.93%), followed by the 20–29 and 50–59 age groups.

Regarding the anatomical location of nerve injuries in the upper limb, most occurred in the forearm (69.72%), followed by the wrist and hand (45.17%).

Of the 776 upper limb nerve injuries, 325 were median nerve injuries (53.19%), followed by ulnar nerve injuries (223 injuries – 36.5%), radial nerve injuries (118 injuries – 19.31%), common digital nerve injuries (102 injuries – 16.69%), and musculocutaneous nerve injuries (8 injuries – 1.31%).

In the studied population, median nerve injuries predominated at the radiocarpal joint (50.57% of injuries at that level), in the forearm (50.2%), and at the elbow (50%). In the arm, most injuries were to the radial nerve (40%). All hand-level injuries involved the common digital nerves.

The primary cause of nerve injury was trauma from angle grinders and other electric tools, such as chainsaws and circular saws (38.46% of cases), followed by glass cuts (32.9%), knife wounds, post-traumatic sequelae, crush injuries, avulsions, contact with non-electric hand tools, and animal attacks.

In terms of seasonal distribution, a higher number of nerve injuries occurred during the warmer months. Summer months accounted for 31.1% of cases, spring and autumn for 25.37%, and winter for 18.17%. The seasonal distribution of electric tool injuries followed a similar pattern, with a more even distribution across autumn (28.94%), summer (27.23%), and spring (26.38%), and the fewest cases in winter (17.45%).

Of all nerve injuries, 75.12% were treated with direct neurorrhaphy, 16.42% with neurolysis, 2.93% with autograft, 4.39% with neurotization, 0.98% with transposition, and 0.16% with nerve conduit reconstruction. Most patients underwent primary repair (507 patients – 83.8%), while 98 patients (16.2%) had secondary repair.

Clinical Study II: Therapeutic Strategies in Nerve Injuries: Current Data and Future Perspectives

We conducted a retrospective analysis of cases admitted to the Plastic Surgery and Reconstructive Microsurgery Clinic of the Bucharest Emergency Clinical Hospital, selecting only patients who had sustained nerve injuries in the upper limb. The analysis focused on a 3-year period, from January 1, 2017, to December 31, 2019.

At the time of admission, all patients gave consent for their medical data to be used for future research purposes. The collected variables included: date of admission, age, sex, involved nerves, associated acute injuries, and the presence of comorbidities. All data were collected and processed using Microsoft Excel, version 16.66.1. The only quantitative variable was the patients' age, for which we calculated the mean, median, and standard deviation.

We identified 734 patients who sustained nerve injuries in the upper limb: 156 were admitted in 2017 (21.25%), 263 in 2018 (35.83%), and 315 in 2019 (42.91%). Of the 734 patients included in the study, 600 (81.74%) were male and only 134 (18.26%) were female. The mean age was 45.81 (±15.23) years, with a median of 46 years. The youngest patient was a 16-year-old boy, and the oldest was a 94-year-old woman.

The most frequently affected nerves in the upper limb were the digital nerves, totaling 785 nerves (80.59%), followed by the median nerve (83 nerves; 8.52%), the ulnar nerve (73 nerves; 7.49%), the radial nerve (31 nerves; 3.18%), and finally the musculocutaneous nerve (2 nerves; 0.21%), summing to a total of 974 injured upper limb nerves.

Some patients presented with multiple nerve injuries, in various combinations, all in emergency contexts. The most common was injury to both digital collateral nerves, found in 27.24% of cases.

There were also associated injuries involving major nerves in our cases. An association between the median and ulnar nerves was observed in 23 patients (3.13%) who presented with trauma affecting both nerves. There were 6 patients (0.81%) with associated injuries of the median and radial nerves. All three major nerves of the forearm (median, ulnar, and radial) were affected in 5 cases (0.68%). We also identified one patient (0.13%) with injuries to both the musculocutaneous and radial nerves. Furthermore, one patient (0.13%) presented with a lower limb nerve injury in addition to the upper limb injury, having both the radial nerve and the common peroneal nerve affected on the same side (ipsilateral).

Out of the 734 patients included in the study, the vast majority benefited from standard nerve repair, which ensures optimal outcomes. However, for some patients, direct neurorrhaphy was not possible due to the size of the nerve defect. We identified 42 such cases, most involving the digital nerves (24 patients; 57.14% of defects), followed by the ulnar nerve (7 patients; 16.66%), the median nerve (5 patients; 11.90%), the radial nerve (3 patients; 7.14%), both median and ulnar nerves (2 patients; 4.76%), and finally the posterior interosseous nerve (1 patient; 2.38%). These nerves were injured at various levels, resulting in differing reconstructive procedures accordingly, as detailed in Table 7.2.

Table 2: Reconstructive Procedures for Nerve Defects at Different Levels

Injured nerve	Level of injury	No. of patients	Reconstructive procedure	No. of procedures
Digital	Digit	19	Spare part nerve graft	6
			Muscle-in-vein conduit	2
			Heterodigital sensate flaps	5
			Nerve transfer from the contralateral non-functional side	6
	Palm	5	Lateral antebrachial cutaneous nerve graft	1
			Spare part nerve graft	3
			Muscle-in-vein conduit	1
Median	Forearm	4	Sural nerve graft	4
	Arm	1	Sural nerve graft	1
Ulnar	Forearm	3	Sural nerve graft	3
	Proximal forearm	4	Ulnar nerve anterior transposition	4
Median + Ulnar	Forearm	2	Sural nerve graft	2
Radial	Arm	3	Sural nerve graft	3
Posterior interosseous	Forearm	1	Lateral antebrachial cutaneous nerve graft	1

Peripheral nerve injuries often result in severe functional deficits, particularly affecting young, active individuals. Primary nerve repair, using microsurgical techniques, is attempted as the first-line therapeutic approach. When a nerve cannot be repaired via direct neurorrhaphy, various options are available for bridging the nerve defect, each with its own indications and advantages: autologous nerve grafting—still considered the gold standard, vascularized nerve grafts, nerve conduits, allografts, and nerve transfers. All these options were encountered in our study group, which included a large number of young, professionally active male patients presenting with significant functional impairments caused by upper extremity nerve injuries—particularly when the lesions were located proximally.

Alternative solutions are currently being explored to cover nerve defects and achieve better functional recovery using accessible resources.

Recently developed nerve conduits, made from combined materials through modern technologies, exhibit good mechanical properties and adequate biological functionality, supporting the nerve regeneration process. Textile technologies represent a promising field, enabling the rapid and cost-effective fabrication of nerve conduits with optimal biological properties.

Clinical Study III: Functional Outcomes Following Nerve Transfers for Shoulder and Elbow Reanimation in Brachial Plexus Injuries

We conducted a retrospective study over a 10-year period (January 2015 – December 2024) in the plastic surgery departments of Zetta Hospital Bucharest, Bucharest Emergency Clinical Hospital and M.S. Curie Emergency Clinical Hospital for Children. The study focused on patients with brachial plexus injuries, selecting only those who underwent surgical treatment involving nerve transfers. Patients lacking complete medical records and those who underwent other surgical procedures for brachial plexus injuries were excluded.

At the initial consultation, a thorough history and clinical examination (general and local) were performed, focusing on identifying specific lesions and functional deficits. Patients were informed about the available treatment options, including the benefits and risks of each approach. Based on this assessment, a personalized surgical plan was devised. Upon hospital admission, all patients gave consent for the use of their medical data for future research purposes.

Collected variables included: patient name, age, sex, lesion location, injury mechanism, time from injury to surgery, follow-up period, type of nerve transfer performed, and motor recovery outcomes.

Guided by the principle that elbow flexion and shoulder function are priorities in reanimation, our patients underwent one or more of the following nerve transfers:

- Spinal accessory nerve to suprascapular nerve (shoulder function)
- Radial nerve fascicle for triceps muscle to axillary nerve (shoulder function)
- Ulnar and median nerve branches to musculocutaneous nerve (elbow flexion)
- Intercostal nerves to musculocutaneous nerve (elbow flexion)
- Contralateral C7 root to musculocutaneous nerve (elbow flexion)
- Spinal accessory nerve to musculocutaneous nerve (elbow flexion)

A total of 37 patients with brachial plexus injuries underwent nerve transfer surgeries between 2015 and 2024. Most were male (34 out of 37); the 3 female patients were children with obstetric injuries. Age ranged from 1 to 77 years, with a mean of 26.8 years. There were 9 pediatric and 28 adult patients.

Regarding the injury mechanism, most adult patients (27 of 28) were injured in road traffic accidents, with over 50% involved in motorcycle accidents (54%). Among pediatric cases, 8 of 9 had obstetric injuries, and 1 had a polyneuropathy caused by a viral infection.

Concerning the injury level, from a total of 37 patients, 18 had complete brachial plexus injuries, and 19 had partial injuries (18 at C5–C6 and 1 at C5–C6–C7). Left upper limb injuries were more common (24 patients; 64.86%) than right-sided injuries (13 patients).

From our total of 37 patients, 34 underwent nerve transfer surgery for shoulder reanimation. All received spinal accessory to suprascapular nerve transfer. Additionally, 4 patients received a medial radial nerve fascicle transfer to the axillary nerve. According to the Medical Research Council (MRC) scale, 85.3% achieved M3 or better shoulder function: 47.06% reached M3, 38.24% M4, 11.76% M2, and 2.94% M1. Combined procedures (spinal accessory nerve to suprascapular nerve transfer and the medial triceps nerve to axillary nerve transfer) resulted in M3 or M4 outcomes in all cases.

Regarding the results based on age groups, we observed that all the children with shoulder function procedures obtained a result of M3 or better compared with 81.48% in our adult population, while 71.43% of children obtained a M4 result, compared with 29.63% of the adults (Figure 9). Furthermore, results in our study showed that 88.23% of the patients with complete injuries gained a result of M3 or better compared with 82.36% of the partial brachial plexus injuries, but 41.18% of them gained a result of M4 or better compared with 35.29% from the complete brachial plexus injury population.

Procedures to restore elbow flexion were done on 32 out of our 37 patients. A total of 29 of them underwent nerve transfer surgery, and 3 of them (all pediatric patients) benefited from C5 root grafting to the upper trunk (2 of them with sural nerve graft and one of them with nerve conduit) and C6 root grafting to the middle trunk with sural nerve graft. The 29 nerve transfer procedures distributed as follows: 13 intercostal to musculocutaneous nerve transfers, 11 ulnar and median fascicles to musculocutaneous nerve transfers, 2 contralateral C7 to musculocutaneous nerve transfers with ulnar nerve graft, 2 spinal accessory to musculocutaneous nerve transfers with sural nerve graft and 1 C7 fascicles to distal C5 and C8 fascicles to distal C6 nerve transfer (in pediatric patient). Among our patients, 84.38% obtained a result of M3 or better according to the

Regarding the surgical technique used for reanimation of the elbow, recovery grades of M3 or M4 were observed in 76.92% of the patients with transfer of the intercostal to musculocutaneous nerve, in 90.91% of the patients with transfer from the ulnar and median fascicles to musculocutaneous nerve, in 100% of patients with transfer of the contralateral C7 to musculocutaneous nerve, in 50% of the patients with transfer of the spinal accessory to musculocutaneous nerve, 100% of the patients with transfer of C7 fascicles to distal C5 and transfer of C8 fascicles to distal C6 nerve and 100% of the C5 root grafting to the upper trunk and C6 root grafting to the middle trunk with sural nerve graft group.

Regarding the results based on age groups, we observed that all of our children population obtained a result of M3 or better, compared with 78.26% in our adult population, and 77.78% of children obtained a M4 result, compared with 43.48% in the adult population.

Concerning the results based on partial vs complete brachial plexus injuries, we found out that the group with partial brachial plexus injuries had a better result compared with the complete brachial plexus injury group (93.33% vs 76.47% of M3 and M4 recovery stages).

In our cohort of 37 patients, the time elapsed between the accident and surgery ranged from 2 to 24 months, with an average of 8.03 months. The mean follow-up time was 3.32 years, ranging from 1 to 9 years.

Experimental Study: Comparative Methods of Nerve Regeneration in Sciatic Nerve Injuries in Rats

This study aimed to compare functional outcomes after creating a sciatic nerve defect in rats and repairing it using three different techniques: autograft (the gold standard, serving as the control group), interposition of a nerve conduit made from the aorta filled with striated muscle fragment, and interposition of a conduit made from the aorta filled with striated muscle and supplemented with processed fat for improved results.

The experimental protocol adhered strictly to current ethical standards for animal research. Following theoretical design, the project received approval from the Ethics Committee.

The experiment was conducted in the biomedical facility of the Bucharest Emergency Clinical Hospital, authorized by the DSVSA.

The experimental model was carried out on 15 white Wistar rats acquired from the Fundeni biobase. Rats were chosen due to the similarity of the sciatic nerve to the human nerve, both histologically and in terms of nerve regeneration. Each animal was housed in a separate cage and was provided with food and water ad libitum, with the bedding being changed daily or whenever necessary. Each rat had an individual file on which information was recorded regarding the weight and the circumference of both thighs before the first surgical intervention and at the end of the study, before the second surgical intervention; the surgical protocols for both interventions; operative times for the two surgeries; and the results after calculating the sciatic functional index (SFI) at 3 and 6 weeks.

The surgical interventions were performed under general anesthesia using Sevoflurane for induction and a mix of 100 mg/kg body weight Ketamine + 10 mg/kg body weight Xylazine (Ketamine dilution: 1 ml Ketamine + 9 ml saline; Xylazine dilution: 0.5 ml Xylazine + 9.5 ml saline), administered intraperitoneally. The required dose was calculated based on the weight of each laboratory animal, measured prior to anesthesia.

The 15 rats were divided into 3 groups, with 5 rats per group as follows: group 1 - nerve autograft, group 2 - interposition of a nerve conduit made from the aorta and filled with a striated muscle fragment, group 3 - interposition of a nerve conduit made from the aorta, filled with a striated muscle fragment and added processed fat.

Under general anesthesia, after shaving the surgical field, with the laboratory animal placed in ventral decubitus, an incision was made on the right lower limb from the level of the knee joint to the ischial tuberosity, followed by dissection exposing the biceps femoris and gluteus maximus muscles. Through an incision in the biceps femoris muscle, followed by its dissection, the sciatic nerve was identified. The sciatic nerve was then sectioned, creating a 0.5 cm nerve defect. After the creation of the nerve defect, repair was performed differently depending on the study group: in **group 1**, the excised nerve segment was flipped and repositioned at the defect site as a nerve graft and sutured at both ends using epi-perineural suturing with Prolene 9.0 thread, in **group 2**, repair was performed using an aortic graft; the aorta was cut to be 2–3 mm longer than the nerve defect, filled with a fragment of striated muscle harvested from the biceps femoris, and sutured at both ends of the nerve defect using Prolene 9.0 thread, in **group 3**, in addition to the technique used in Group 2, processed fat (nano fat) was added. The aortic grafts and fat were harvested from a control group rat after the monitoring period and after it was sacrificed for the purpose of harvesting a nerve fragment for histopathological analysis. After nerve suturing, the area was washed, hemostasis was performed, muscle planes were closed with Vicryl 4.0, and the skin was sutured with Prolene 4.0. Subsequently, the area was cleaned with Betadine, and antimicrobial ointments were applied along the suture line.

No rat died either immediately postoperatively or later. Regarding postoperative complications, only 2 cases of partial wound dehiscence and minor self-inflicted injuries—especially at the plantar level—were recorded, all of which healed spontaneously. The rats were monitored daily over a period of 6 weeks during which they were provided with full comfort, including free access to water and food, bedding changed as often as necessary, a 12-hour light/dark cycle, and constant temperature and humidity.

Over the course of the 6 weeks, a series of tests were conducted to evaluate nerve regeneration. Before each surgical intervention (week 0 and week 6), the weight and the circumference of both thighs were measured. The walking footprint test was performed at 3 and 6 weeks, and the sciatic functional index (SFI) was calculated. At 6 weeks, a swimming test was performed in which the rat was placed in a water container for one minute, during which it was filmed in slow motion to count the number of strikes per minute performed by both back feet to stay afloat. At the end of the follow-up period, the rats were sacrificed, and a nerve fragment along with 0.5 cm proximally and distally to the anastomosis was harvested for histopathological analysis.

The surgical intervention was performed in all cases on the right lower limb. Regarding weight evolution in the first group, the average preoperative weight was 409.6 grams, and at 6 weeks it was 528.4 grams, with a weight gain of 118.8 grams. In group 2, the average weight before the first surgery was 453.4 grams, and 501.6 grams at 6 weeks, resulting in a difference of 48.2 grams. In group 3, the average initial weight was 435.2 grams, the average at 6 weeks was 515.6 grams, and the difference was 80.4 grams.

In terms of operative times, the average across the three groups was as follows: group 1 - - 57.2 minutes ± 5.11, group 2 - 50.4 minutes ± 3.84, group 3 - 51.2 minutes ± 3.49.

Regarding the circumference of the right thigh, between the preoperative moment and after 6 weeks, an average decrease in the circumference of the operated thigh was observed as follows: 4.4 mm ± 1.516 in the autograft group, 4.2 mm ± 1.483 in the group with aortic conduit and muscle, 4 mm ± 2.549 in the group with aortic conduit, striated muscle fragment, and processed fat. The mean, median, and dispersion were quite similar across the three groups. The Shapiro-Wilk test showed a normal distribution of the data ($p > 0.05$), while the ANOVA test indicated that there were no statistically significant differences between the three groups regarding the change in thigh circumference.

As for the swimming test, a mean difference in the number of strokes per minute between the operated and non-operated limb was observed as follows: 3.6 ± 1.14 strokes per minute, median 4 strokes/min in the autograft group, 5 ± 1.2247 strokes per minute, median 5 strokes/min in the aortic conduit and muscle group, 3.2 ± 0.836 strokes per minute, median 3 strokes/min in the group with aortic conduit, muscle, and processed fat. A slightly better mobility was observed in the group with the aortic conduit filled with muscle and processed fat, followed by the autograft group and the aortic conduit with muscle group. Here too, the Shapiro-Wilk test confirmed normal data distribution ($p > 0.05$), while the ANOVA test showed a trend toward group differences, but the sample sizes were too small for a definitive conclusion ($p = 0.0518$).

At 3 and 6 weeks, each rat underwent walking tests and the Sciatic Functional Index (SFI) was calculated. The values of this index range from 0 to -100, with 0 representing normal function and -100 complete loss of function. Improved function of the operated lower limb was observed in all three groups. SFI at 3 weeks was as follows: group 1: -67.446 ± 1.1113 (a 67.46% functional deficit), group 2: -67.662 ± 5.9840 (a 67.66% functional deficit), group 3: -55.886 ± 5.3878 (a 55.89% functional deficit). At 6 weeks, the deficits decreased to 46.10% in group 1, 51.48% in group 2 and 44.59% in group 3. The best function was achieved by the rats in the group with the aortic conduit filled with muscle and processed fat, closely followed by the autograft group, while the group with the aortic conduit filled with muscle alone had the weakest outcome. The Shapiro-Wilk test showed normal data distribution. ANOVA indicated statistically significant differences between at least two of the three groups ($p = 0.0059$). The Tukey HSD test revealed statistically significant differences between: the autograft group and the aortic + muscle group ($p = 0.0282$), the aortic + muscle + fat group and the aortic + muscle group ($p = 0.0063$), with no significant difference observed between the autograft group and the aortic + muscle + fat group ($p = 0.689$). This confirms better nerve regeneration in the groups treated with autograft and aortic conduit, muscle and fat compared to the aortic conduit and muscle group.

At the time of harvesting the sciatic nerve, adhesions were observed between the nerve and the surrounding muscle mass in all 15 rats. After dissection, the appearance of the sciatic nerve under the optical microscope was examined for the three study groups. No neuroma formation or anastomotic ruptures were observed in any of the subjects. No differences were observed in nerve diameter across the three studied groups.

Microscopic examination of the slides revealed marked nerve regeneration in all three groups, with well-represented nervous tissue. Between Group 1 (autograft) and Group 3 (aortic conduit filled with striated muscle fragment and processed fat), no significant differences were noted; both groups showed good regeneration, with organized, well-represented nervous tissue, many myelinated axons—especially visible in cross-sections—numerous blood capillaries, and many Schwann cells. In Group 2 (aortic conduit filled with striated muscle fragment), good nerve regeneration was also observed, with a significant amount of well-represented nervous tissue, but with a more pronounced presence of connective tissue interspersed among the nerve fibers.

Preliminary Experimental Study

As in the previous study, the protocols and current regulations regarding the ethics of experimental research on laboratory animals were respected. The group consisted of 10 adult specimens. The interventions were performed under general anesthesia, in accordance with the institutional protocol presented in the previous study. Preoperative preparation was carried out in the same manner as in the previous study.

For each subject, an incision was made on the posterior thigh, the sciatic nerve was exposed, a segment of the sciatic nerve was resected, and a 0.5 cm nerve defect was induced. The defect created was repaired by interposing a composite graft consisting of a collagen conduit pre-filled with autologous striated muscle fibers. The surgical technique used for inducing the nerve defect and interposing the composite graft is detailed below:

After anesthesia and preoperative preparation, with the laboratory animal positioned in ventral decubitus, an incision was made on the right lower limb from the level of the knee joint to the ischial tuberosity, followed by dissection to expose the biceps femoris and gluteus maximus muscles. Through an incision in the biceps femoris muscle, followed by its dissection, the sciatic nerve was identified. The sciatic nerve was then sectioned, creating a 0.5 cm nerve defect. The collagen conduit was cut 2–3 millimeters longer than the defect to allow tension-free suturing and was filled with striated muscle fibers harvested from the biceps femoris muscle. After creating the defect, it was repaired by interposing the collagen conduit. The nerve conduit was then sutured at both ends of the nerve defect using Prolene 9.0 suture. After nerve suturing, lavage and hemostasis were performed, muscle layers were closed using Vicryl 4.0, and the skin was sutured using Prolene 4.0. Finally, the surgical site was cleaned with Betadine and antimicrobial ointments were applied along the suture line.

Postoperative monitoring was conducted under the same conditions as in the first study. For functional evaluation in the studied group, the Sciatic Functional Index (SFI) was assessed in all 10 rats at 6 weeks postoperatively. At the same time point, one specimen was euthanized and sent to a specialized laboratory for detailed histopathological analysis, in order to establish a reference framework for interpreting the future analyses of the remaining group.

The remaining 9 rats were monitored long-term. Functional reassessment using the Sciatic Functional Index (SFI) was performed at 8 months. At the end of the observation period, the entire remaining group was sacrificed, and the harvested tissues were subjected to histopathological analyses.

The mean preoperative weight was 423.5 grams, with a standard deviation of 37.807 g. Regarding operative time, the average was 50.4 minutes ± 6.275. The mean value of the sciatic functional index at 6 weeks was -56.959 ± 11.8, indicating a functional deficit of 56.959%. At 8 months, the mean sciatic functional index was -48.656 ± 8.15, indicating a functional deficit of 48.656%.

In the rat sacrificed at 6 weeks, the macroscopic examination revealed significant narrowing in the caliber of the collagen conduit, particularly in the central region.

Microscopically, the images show the presence of crystallized materials, collagen remnants, and significant inflammatory infiltrate. However, nervous tissue is also visible, with axons surrounded by myelin sheaths and Schwann cells.

At 8 months, microscopic examination showed optimal nerve regeneration, with well-represented nervous tissue and no signs of inflammation, indicating good tolerance to the foreign material used in the conduit. Organized nerve growth could be observed, with axons visible in both longitudinal and cross sections.

Conclusions and Personal Contributions

The doctoral thesis comprises an extensive study, structured into two major components: a diverse clinical part and an experimental one, aimed at investigating the complexity of peripheral nerve injuries from a multidimensional perspective. We focused especially on nerve injuries affecting the upper limb, considering their high frequency, the significant functional impact they generate, and the major consequences on patients quality of life, particularly among young individuals. We also examined the potential for functional recovery and the possibility of socio-professional reintegration—essential aspects in the management of these conditions.

The activity carried out within the Bucharest Emergency Clinical Hospital provided access to a very rich case database, which formed the basis for the retrospective clinical study conducted over a period of nine years. This setting allowed for a detailed characterization of peripheral nerve injuries, which occurred mainly in post-traumatic contexts. We placed particular emphasis on major injuries located in the arm and forearm, considering their significant functional impact. Following the analysis, we succeeded in outlining the complexity of these injuries and identifying the main directions in which further research is necessary, both clinically and experimentally.

We also performed a thorough analysis within the second retrospective clinical study, focusing both on the distribution of the injuries and the characteristics of the patient group, as well as on the therapeutic strategies applied in our clinic. We evaluated all treatment protocols used, taking into account the particularities of each case, depending on the nature and complexity of the injury. This approach allowed us to highlight current therapeutic trends and identify aspects in need of optimization in current clinical practice.

The third clinical study focused on brachial plexus injuries, the most severe form of peripheral nerve trauma in the upper limb. These injuries lead to severe paralysis, associated with a high degree of disability and a reduced potential for functional recovery. Currently, the therapeutic approach centers on nerve transfers, with the goal of restoring the essential functions of the affected limb. The interventions primarily aim at functional reconstruction of the shoulder and elbow—key components for regaining a minimum level of motor autonomy.

Both the specialized literature and the studies conducted in our clinic highlight a high incidence of nerve injuries that result in major functional deficits. A remarkable and consistently observed aspect is the lack of predictability in terms of functional recovery, even when the surgical intervention is correctly performed. Even when advanced microsurgical techniques are applied, with dissection under surgical loupes and nerve suturing under the microscope by highly experienced teams, functional outcomes often remain unpredictable.

This variability can be attributed to both intrinsic patient factors—such as age, type of injury, and associated comorbidities—and extrinsic factors, such as the patient's access to postoperative care, adherence to prescribed follow-up schedules, and involvement in a sustained medical rehabilitation program. Recovery in such cases requires months of physical therapy, including electrostimulation, and demands close collaboration between the plastic surgeon, rehabilitation physician, and physiotherapist.

The therapeutic plan is tailored according to the patient's residual deficits and progress and is complemented by procedures such as immobilization in functional positions, early motor reeducation, and occupational therapy, all customized to meet the individual needs of each patient.

Current international research is focused on identifying modern therapeutic solutions aimed at improving surgical outcomes in peripheral nerve reconstruction. An emerging field is bioengineering, which seeks to develop products capable of stimulating nerve regeneration, as well as artificial nerve conduits that can be used in the reconstruction of nerve defects. Although such devices are already approved and successfully used in international centers, their high acquisition cost remains a major barrier to their widespread implementation in Romanian medical institutions.

Considering this limitation, we saw an opportunity to initiate research partnerships with Romanian technical institutions aimed at developing nerve conduits that are biocompatible, accessible, and efficient, especially for small-sized nerve defects such as those affecting digital nerves—a pathology frequently encountered in our clinical practice. In this context, we collaborated with the Leather and Textile Institute and we are currently engaged in an international multidisciplinary partnership with the Politehnica University of Bucharest and other technical universities abroad.

In a translational research approach, we aimed to develop an experimental platform that would allow testing various solutions for nerve defect replacement. We also proposed a preliminary experimental model, with the potential to become a surgical standard for the evaluation and development of accessible nerve conduits at the national level.

Last but not least, a significant contribution is the exhaustive analysis of the specialized literature, in which we evaluated all current treatment strategies for peripheral nerve injuries, as well as new techniques for stimulating nerve regeneration. This thorough analysis enabled us to formulate a set of conclusions integrated with the data obtained from our clinical and experimental studies, leading to the development of an extended therapeutic algorithm. This algorithm has the potential to guide the plastic surgeon in making therapeutic decisions in the treatment of peripheral nerve injuries, adapting the strategy to the type, location, and severity of the lesion.

We also identified modern, internationally approved techniques and analyzed the feasibility of introducing them into Romanian medical practice, depending on existing technical and infrastructural possibilities. However, certain categories of injuries continue to pose major therapeutic challenges, such as extensive proximal injuries, massive tissue destruction, crush injuries, multiple peripheral nerve involvement (including brachial plexus injuries), and defects secondary to complex tumor excisions. For these situations, standardized therapeutic options remain limited and require further research.

An innovative direction we aim to develop within institutional partnerships with technical universities in Romania is the integration of artificial intelligence in the field of peripheral nerve surgery. This could contribute both to predicting postoperative functional recovery and to individualizing and monitoring rehabilitation programs, thereby optimizing the therapeutic journey of our patients.

In this context, we developed a strong partnership with the team from the Medical Rehabilitation Department of the hospital, consisting of a physician specialized in physical and rehabilitation medicine, as well as physiokinetotherapists with extensive experience in managing peripheral nerve injuries. This collaboration enabled the implementation of standardized rehabilitation protocols, focused on achieving the fastest possible functional recovery and facilitating the patients socio-professional reintegration.

Patients are integrated into the rehabilitation team from the period of hospitalization, with constant communication between the surgical team and the rehabilitation team. At the end of each rehabilitation treatment cycle, the patient is re-evaluated by the plastic surgeon, and the subsequent directions of the rehabilitation program are determined in an interdisciplinary manner.

In addition, patients benefit from regular neurological evaluations, repeated electromyographic investigations, and specialized imaging to monitor the progress of nerve regeneration. In collaboration with imaging specialists, we conduct ultrasound assessments of peripheral nerves, especially using soft tissue ultrasound. This segment is still in an early stage of development, without fully standardized results, but with significant potential for the objective monitoring of nerve regeneration.

We considered it essential to maintain continuous communication with the patient, both through periodic medical visits and modern online communication methods. Especially for patients from other counties, we encouraged constant reporting of functional progress through the submission of photos and videos of the affected limb. We also encouraged patients to ask questions regarding postoperative evolution and the progress of the rehabilitation program. This active communication aimed to increase adherence to the prescribed treatment and improve functional outcomes through continuous and personalized monitoring of the therapeutic process.

In conclusion, this doctoral thesis reflects a complex and integrated approach to peripheral nerve injuries, combining rigorous clinical research with experimental innovation and interdisciplinary collaborations. The results obtained highlight both the major challenges associated with the treatment of these injuries and the promising directions for improving functional prognosis. Through the development of national and international partnerships, the implementation of modern technologies, and the integration of artificial intelligence, real prospects are emerging for the personalization of therapies and the enhancement of medical care quality.

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