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*The role of the neurological growth factor in the nervous
regeneration after the sectioning of the
peripheral nerves*

PhD THESIS RESUME

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HYPOTHESIS OF WORK AND GENERAL OBJECTIVES

Whether we're talking about plastic surgery or other such fields, surgeons often face peripheral nerve injuries, even if they're represented by emergencies or chronic patients.

When it comes to emergencies, it is frequent to make contact with complete or incomplete injuries through sections at the E.R.

Undiagnosed nerve injuries after a laceration are pretty frequent (Grobnicu O, 2018). The consequences, as the sensory deficit, neuroma and type I complex regional pain syndrome, could be severe.(Wojtkiewicz DM, 2015).

At the laceration in the palm of a hand, for instance, diverse evaluation and research methods have been conducted regarding the cutaneous sensitivity and sensory deficit. Although it's the most commonly used, the cassette test has less than 100% sensitivity and specificity. Some authors have recently shown that other usual tests' sensitivity and specificity don't even reach 100% (Weber static test, Weber dynamic test, the Semmes Weinstein monofilament test). Most authors still believe that any laceration at the level of a hand, nearing a nervous structure, must be surgically explored.(Grobnicu O, 2018).

In the case of surgical exploration and highlighting a complete section, with no defects, of a peripheral nerve, the most frequently seen case, the microsurgical nervous suture technique is approached most. Over the years, this technique has evolved, and, in the present, a plastic surgeon with experience in microsurgical technique can conduct a perfect neurorrhaphy, from a technical point of view. All things considered, long term results aren't always satisfactory, functionally speaking. (Grinsell D, 2014)

Currently, various studies are researching to improve the functional answer after a peripheral nervous injury, enhancing, at the same time, patients' quality of life.

Being deeply interested in the microsurgical field of plastic surgery, I followed an university class in Strasbourg (France) to smoothen my microsurgical technique. As a result of this 1 year length class , I received the microsurgery university diploma from Strasbourg (Annex 1). This opportunity augmented my need to continue my research regarding microsurgery.

In the meantime, I also studied specialized literature, to underline the new current researches regarding peripheral nervous functionality relief and I have noticed that there's

no such thing as a specific practice or an international consensus of a nervous suture adjuvant protocol for regeneration and a well established, worldwide uniformed recovery protocol.

Thus, by studying the specialized literature, I came to the realization that various universal centers have tried to find a way to improve nervous regeneration via diverse methods. Present-day researches focus on the introduction of certain molecules at the moment of the neurorrhaphy, or from distance, or continuously during a certain period. Plenty of molecules have been studied, the neurological growth factor (NGF) being one of them, which has been studied as a regeneration factor by being inserted at the level of the nervous suture, on a subcutaneous or intramuscular level. (Sciboz OC, 2021).

The originality of this study is represented by the way of introducing this substance at epiperineural level at the end of the microsurgical suture.

GENERAL RESEARCH METHODOLOGY

Considering the specialized literature, laboratory animal studies and microsurgery improvement principles of evaluation, I have conducted an experimental research study, following the comparison between 2 lots of sciatic nerves on a rat, introducing a different substance at the epiperineural level.

It has been distributed to the 2 lots in the following way:

1. Complete nervous section (sciatic right side), microsurgical suture, introduction of NaCl 0.9%
2. Complete nervous section (sciatic right side), microsurgical suture, introduction of β -NGF.

At the end of the study, 10 left side sciatic nerves, without nerve injury, have been sent for a histopathological study to have the structure of an injury free nerve as guidance.

To be accepted, the research project has to meet various criteria in order for it to be carried out in accordance with the current law concerning scientific research. All the steps to achieve the research study authorizations have been followed. All the practical procedures on laboratory animals have respected the Helsinki declaration of 1975 as revised in 2008.

In order to elaborate a research study in vivo (meaning in the living organism), various medical ethics and laboratory animal safety criteria are necessary.

The study approval in a primary stage has been decided by the Ethics Commission, which evaluates the project scientifically. The next step was to make the file for the study authorization by Direcția Sanitară Veterinară și pentru Siguranța Alimentelor (DSVSA)/Sanitary Veterinary and Aliments Safety Direction, which has been in the project's favor.

The study realisation space has been assigned by Spitalului Clinic de Urgențe Floreasca București (Clinical Emergency Hospital Floreasca Bucharest) within their research Biobase headquarters.

The description of this project's objectives is marked by the potential benefits it may bring, more specifically the fact that the positive results of this study could not only relieve peripheral nerve sensitivity, but also the motor function, important matters regarding nerve injury.

The laboratory animal species used, The Wistar Rats, an albino rat from the *Rattus Norvegicus* family, has been chosen because they have been specifically designed for laboratory animal studies, are easy to manipulate, kind and show physiological and anatomical similarities with the human species, knowing that 99% of their DNA is similar to the human one. (Krinke GJ, 2000).

The number of animals accepted has been reduced to the minimum necessary to have available positive results with statistic value, in accordance with the ethical rules(3R: Reducere, Rafinare, Inlocuire-Replace/3R: Reduce, Refine Replace)(Kirk RGW, 2018).

CHAPTERS SYNTHESIS

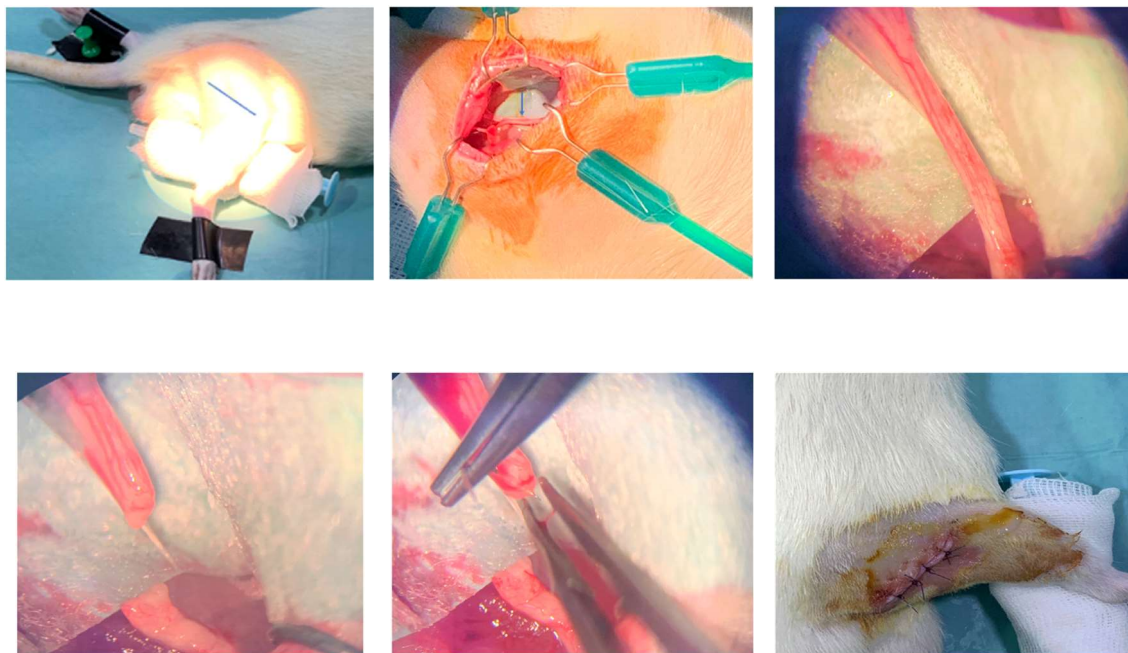
The experimental study debuted with the anesthesia of the laboratory animals. All the steps for the preparation of the anesthesia have been guided by the protocols described in the book „Laboratory Animal Anaesthesia – Paul Flecknell”. (Flecknell PA, 1993).

The administration mode chosen for this study was the intraperitoneal one, due to its convenient execution and the expected anodyne, muscular and visceral reflex relaxation effect.

For this study, I used the classic intraperitoneal clinic anesthetic proposed by the European Guides for the Wistar Laboratory Rats, composed of a mix of Ketamine 50mg/ml and Xylazine 2%. The injectable solution was made with 1 ml Ketamine for 0,15 ml

Xylazine, adding physiological serum up to 2,5 ml solution. (Anesthesia for Minor Procedures. Research animal training. 2020; Smith AC, 1994).

After the rat has been anesthetized, the preparation of the surgical field was made and, further on, its incision and dissection at the right thigh level, incision focused on the right side sciatic nerve's projection point. After highlighting the right side sciatic nerve, the transverse sectioning of the nerve and the neurorrhaphy under the optical microscope is practiced. (Images have been extracted from my personal PhD thesis)



The substances are being introduced. To the first lot of 10 animals, a quantity of 0,1 ml of physiological serum has been injected in the epineurium-perineurium area, using a 0,5 ml syringe with 32GX8mm calibrated needle.

The introduction of the needle has been conducted under microscopic observation, between 2 suture points in the area closest to the epineurium vascularization. To the second lot, the same quantity as the physiological serum of β -NGF has been injected using the same technique that has been previously described.

The cutaneous suture is practiced. Post-surgery, the rats are kept and taken care of in separate cages, fed and hydrated ad libidum.

After 4 weeks, a motor regeneration evaluation is conducted (walking index footprint of sciatic functionality, EMG, measurements of the thigh circumference) and the evaluation of the cutaneous sensitivity using the Semmes Weinstein monofilaments.

The same day, a second surgery is conducted in order to be able to achieve the histopathological analysis of the neurorrhaphy. The neurorrhaphy sectioning is practiced at a proximal and distal distance of 0.5 cm from it. The distal end of the neurorrhaphy is marked with a surgical wire for orientation.

The components are sent for anatomopatologic study in vials containing 2% swabbed glutaraldehyde.



In the end, we follow the International Guides (Guidelines for the euthanasia of animals, 2020) to eutanasiate the laboratory animals.

The statistical analysis has been conducted, using IBM SPSS Statistics 25 si Microsoft Office Excel/Word 2013.

The histologic analysis has been evaluated under an electronic microscope, range within 200X. The histological images have been edited in Software ImageJ.

FINAL CONCLUSIONS AND PERSONAL CONTRIBUTION

Final Conclusions

2. The β -NGF substance introduced at the epineurium level brings improvement to the peripheral nerve regeneration after a neurorrhaphy nerve sectioning in comparison with the introduction of a saline solution (NaCl 0,9%).

3. Four weeks after the neurorrhaphy and β -NGF introduction, the cutane sensitivity is substantially ameliorated considering the cutane sensitivity of the rats treated with nerve suture and saline solution after a nerve sectioning.

4. The lot of rats treated with saline solution show a degree of contralateral muscle hypertrophy, as a result of the partial muscle atrophy at the level of the operated thigh.

5. There is no scientific statistical difference between the 2 lots' operated leg automutilation. These injuries can be interpreted as either the lack of the cutane sensitivity, which didn't cause pain at the moment of injury, or a distal nerve pain.

6. The sciatic nerve index highlights a better muscle recovery in the group treated with β -NGF than the group treated with PS.

13. The histopathological report underlines, first of all, a high rate of neo-angiogenesis nerve suture distal on behalf of the lot treated with β -NGF. The neo-angiogenesis may favor peripheral nerve regeneration.

14. Another histopathologic aspect that has been concluded is the appearance of the conjunctive tissue, more prominent in the lot that has been treated with PS, which indicates that there's a bigger nerve fibers (axon) disorganization in this lot. The nerve tissue is better represented in the lot that has been treated with β -NGF .

15. The nerve diameter at the nerve suture level doesn't show significant statistical differences between the 2 lots.

16. There were no signs of neuroma reported in either lot.

17. Nerve suture adherences have been reported for both constant manner lots.

18. At the nerve suture level, no gaps have been found, even if the rats were not restrained at the operated inferior member level. This can bring the conclusion that if there's no tension at the nerve suture level, restraining the affected inferior member will not bring any benefits. But the conclusions are limited to the fact that rats with a restrained operated inferior member haven't been included in this study to be able to distinguish the benefit.

Personal Contributions

This research has been created step by step and it's the labour of systematic work. After the first year of doctoral studies, during which the researches foundation has been established under the university's guidance, the following stages consisted in literature found in an informative database and library books research. The literature data collecting process, their interpretation, organizing them on categories and assimilating and processing the information is necessary, hard work corresponding to the scientific research headquarters before beginning an experimental study.

The microsurgical techniques smoothening and the laboratory animals study has been conducted under a university diploma at the University of Strasbourg, France.

The idea of making a PhD thesis based on the study of peripheral nerves was a relevant one as my curiosity was drawn to the fact that even if the microsurgical technique had evolved in time, the peripheral nerve regeneration was often imperfect. Thus, I studied the literature about adjuvant molecules in the regeneration process, NGF being one of them.

During the same period, I also published 2 articles, for which my interest was focused on nerve regeneration interpretation methods and to emphasize all the specialized articles containing information about the NGF molecule.

The idea of adopting the Von Frey monofilaments, was an inedit one as it represents a new method of interpreting results in the current studies about experimental studies on rats. This is a slightly subjective and easy to execute method.

The brand new element of the study is brought by the manner in which a substance is inserted, the quantity and concentration to create an adjuvant protocol within the peripheral nerve suture. In fact, the idea was that regardless of the fact that the substance can spread on the neighboring tissue after the local injection, a minimum quantity acting on a epiperineural level could help in nerve regeneration.

To conclude, the general and the special part of this PhD thesis have beenbuilt upon a personal contribution through the implication of all theoretical and practical research sources, step by step.

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