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THE ROLE OF NGF IN THE REGENERATION OF PERIPHERAL NERVE INJURY – SYSTEMATIC REVIEW – IMPLICATIONS FOR THE PROVISION OF DAYS OF MEDICAL CARE AFTER PERIPHERAL NERVE INJURIES

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Abstract: The peripheral nervous system has a great repair capacity after injury but the regeneration after peripheral nerve injury is often unsatisfactory [1]. Depending on the size of the defect, these lesions may be treated with primary repair, nerve transplantation or nerve transfer [2].

The clinical results show poor function deficits even if the micro-surgical suture is done in the best conditions [3].

Several adjuvant strategies to repair are currently being developed to speed up the recovery of nerve conduction. The neuronal growth factor is one of the growth factors that could affect nerve regeneration [4].

The aim of this work is a systematic review of the literature on the effects of neuronal growth factor (NGF) as an adjunct to peripheral nerve regeneration.

The speeding up of the healing process after traumatic injuries leads to the modification of the healing and recovery period with the reducing time of medical care with implications in forensic medicine.

Keywords: peripheral nerve regeneration, neuronal growth factor, NGF, nerve recovery.

INTRODUCTION

After a peripheral nerve section, despite rigorous microsurgical repair, only 30-70% of the nerve function is recovered [5]. The nervous injury by section is an economic and social problem by the sequels that prevent the normal course of activities of daily life and create a permanent handicap [6].

The prognosis of this nerve section depends on the time of care that includes the time of diagnosis sometimes not obvious. After diagnosis, proper nerve repair is crucial to getting the best results [7]. Normally the repair of a nerve section can be done in two ways. Either a direct repair with stitches, or an indirect repair with a nerve regeneration guide that connects the two ends of the nerves [8]. Nowadays several adjuvant strategies to repair develop to accelerate the recovery of nerve conduction [9]. The neuronal growth factor is one of the growth factors that could affect nerve regeneration [10]. The aim of this work is to make a systematic review of the literature on the effects of neuronal growth factor (NGF) as an adjunct to peripheral nerve regeneration.

Neuronal growth factor

NGF is a polypeptide of the family of neurotrophins that is required for neuronal development and function by its neurotrophic role [11, 12]. Its action is based on the binding of pro TrkA as well as p75NTR [13]. It was first identified in 1956 by Rita Levi-Montalcini and Stanley Cohen. This discovery was awarded the Nobel Prize for Physiology in Medicine in 1986 for its effects on the pancreas [14] (Fig. 1).

MATERIAL AND METHODS

A search on Medline between 1972-2021 with keywords ("Nerve Growth Factors" [Mesh]) and

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"Peripheral Nerve Injuries" [Mesh] yielded 1596 studies concerning central and peripheral nerve regeneration, which include various growth factors being tested on the nerves. 531 studies found concerning NGF and peripheral and central nerve regeneration that were published between 1989-2021. The articles included in the study describe the use of NGF compared to non-use of NGF. Articles using other growth factors were not considered.

To answer our question about the influence of NGF and its effects on nerve regeneration, the results were limited to articles that discussed the functional results of nerve repair with NGF and without NGF. Only articles in English were considered.

RESULTS

A total of 50 studies were in agreement with the inclusion criteria defined for this research. All written studies have concluded that NGF stimulates peripheral nerve regeneration, which can speed up function recovery. The studies are experimental studies done *in vivo* on laboratory animals.

Figure 1. 2.5S NGF for mice [15].

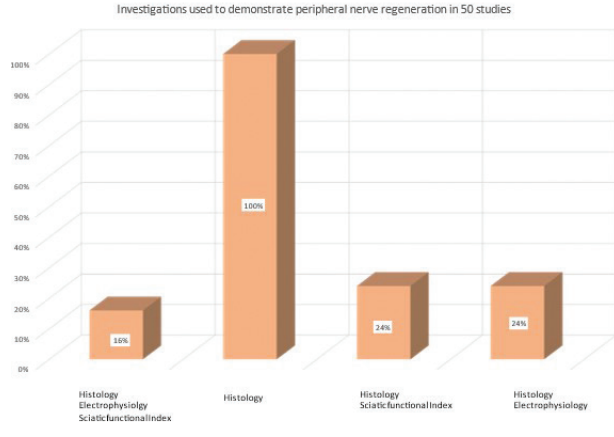

Figure 2. Investigations used to demonstrate peripheral nerve regeneration in 50 studies.

In 50 studies, after peripheral nerve injury, 100% used histological study as evaluation criteria for the nerve regeneration (axonal count of distal nerve segments, nerve diameter) and only 16% of studies used all the evaluation criteria: Nerve histology, electrophysiological values (at a predetermined postoperative time) and Sciatic functional index (Fig. 2). Nerve histology after peripheric crush injury and introduction of NGF recovery better that introduction of saline solution after 6 weeks [16, 17].

Functional recovery after delayed nerve repair even if introduction of NGF by collagen stimulation and nerve conductors predict a low recovery [18, 19].

The predetermined postoperative time to study the results was in 60% of the studies at 4 weeks [20, 21], the other authors studied at less than 4 weeks [22, 23], and others more than 4 weeks old [24, 25] (Fig. 3).

Siri *et al.* [26] concluded that there was no obvious effect of NGF administration on the sciatic nerve of the rat at 4 or 8 weeks after a nerve injury because there is no histological differences between the application of NGF and the absence after 4 weeks after nerve suture. Some authors approve that just local administration of NGF around the nerve repair of a nerve section is necessary to improve the nerve recovery [27, 28]. Others, that a better results of functional recovery is attempt if utilise of additional maintaining molecule around the nerve stiches [29, 30].

DISCUSSION

One of the authors, De Santos *et al.*, found that NGF increases angiogenesis without improving nerve regeneration [31]. The study compares electromyographic findings, action potentials of EMG,

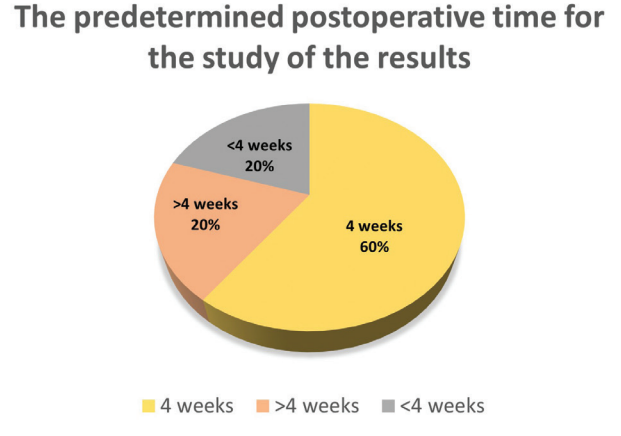

Figure 3. The predetermined postoperative time for the study of the results.

nerve diameter, thickness of myelin sheath, number and diameter of myelinated axons after nerve section, direct microsurgical suture with and without NGF for 6 groups of Swiss Webster mouse. The study concluded that there are no differences from nerve regeneration but differences from angiogenesis. None of the others studies confirms this.

Tom Chao *et al.* [32] using multiple doses of NGF, concluded that an optimal concentration exists when 800 μg/L of NGF is administered locally after nerve suture. Other authors (Lee *et al.*) [33] using concentrations of 5, 20 and 50 ng/mL showed a more potent effect in concordance of 20 and 50 ng/mL [34].

Long-Sun Ro *et al.* [35], Albert Derby *et al.* [36] and Rich *et al.* [37] concluded that also the sensory function is superior for the group using NGF and the group without NGF.

Hailong Yuen *et al.* [16] demonstrated that controlled release NGF microspheres are able to enhance peripheral nerve regeneration through short nerve defects better than NGF alone in nerve damage by crushing because of diffusion and rapid deactivation in extracellular fluids, it is difficult to maintain NGF at the injured sites, which limits the healing effect.

Sencar *et al.* [38] found that a new therapy by combined of NGF and betamethasone subcutaneously injected into the lesion area of the treatment groups three times during the first day may be an effective approach for the treatment of peripheral nerve injury.

Jie Qin *et al.* [39] in 2016 demonstrated that concentrated growth factor promoted SC proliferation and secretion of neurotrophic factors in vitro and improved functional nerve recovery after injury *in vivo*, suggesting that concentrated growth factor provided a way to regenerate iatrogenic nerve damage caused by dental implants. Same conclusion it's related from the study of Lu Y et all in 2019 and Fang Z *et al.* [40, 41].

Quin J *et al.* [42] and Shao H *et al.* [43] noted that concentrate growth factor is a promising candidate biomaterial for peripheral nerve regeneration, and may potentially be utilized to repair nerve injuries.

Authors have concluded that NGF surgical glue promotes nerve regeneration after microsurgical nerve suture, better than glue alone [21] [44], others have shown that fibrin matrix with NGF can help with peripheral recovery nervous [45, 46], others utilise the heparin-poloxamer hydrogel and NGF after peripheral nerve injury with good functional recovery [47, 48].

In conclusion, there are many obstacles that can prevent successful nerve regeneration after a section in the peripheral nervous environment [49, 50]. Most studies using neuronal growth factor to accelerate peripheral nerve function have concluded that NGF promotes functional nerve recovery *in vivo* in experimental studies and reduce nerve allodynia [51, 52].

Probably in the future NGF will be introduced into the treatment protocol, in clinical practice to promote peripheral nerve regeneration after lesions leading to reduced healing and recovery time with implications in forensic medicine.

Conflict of interest

The authors declare that they have no conflict of interest.

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