End-to-side nerve neurorrhaphy: critical appraisal of experimental and clinical data

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Summary

End-to-side neurorrhaphy (ESN) or terminolateral neurorrhaphy consists of connecting the distal stump of a transected nerve, named the recipient nerve, to the side of an intact adjacent nerve, named the donor nerve, “in which only an epineurial window is performed”. This procedure was reintroduced in 1994 by Viterbo, who presented a report on an experimental study in rats. Several experimental and clinical studies followed this report with various and sometimes conflicting results.

In this paper we present a review of the pertinent literature. Our personal experience using a sort of end-to-side nerve anastomosis, in which the donor nerve is partially transected, is also presented and compared with ESN as defined above.

When the proximal nerve stump of a transected nerve is not available, ESN, which is claimed to permit anatomic and functional preservation of the donor nerve, seems an attractive technique, though yet not proven to be effective. Deliberate axotomy of the donor nerve yields results that are proportional to the entity of axotomy, but such technique, though resembling ESN, is an end-to-end neurorrhaphy.

Neither experimental or clinical evidence support liberalizing the clinical use of ESN, a procedure with only an epineurial window in the donor nerve and without deliberate axotomy. Much more experimental investigation needs to be done to explain the ability of normal, intact nerves to sprout laterally. Such procedure appears justified only in an investigational setting.

Keywords: End to side coaptation; neurorrhaphy; epineural window.

Introduction

End-to-side neurorrhaphy (ESN) or terminolateral neurorrhaphy consists of connecting the distal stump of a transected nerve, named the recipient nerve, to the side of an intact adjacent nerve, named the donor nerve, when only an epineurial window is performed [34]. The cut end of the recipient nerve, therefore, is just put against the intact perineurium of the donor nerve. The technique has been utilized since the late XIX century, though it was abandoned with the introduction of microsurgical techniques when end-to-end nerve coaptation became the standard method of nerve repair. The procedure was reintroduced in 1994 by Viterbo et al. [34], who presented a report on an experimental study in rats. Several experimental and clinical studies followed this report with various and sometimes conflicting results.

In this paper we review the available data on ESN and its possible anatomo-physiological bases. Experimental and clinical applications are presented and discussed.

Anatomo-physiological bases of ESN

Since its reintroduction by Viterbo et al. [34], ESN has been extensively studied and various questions have been raised, mostly concerning its anatomo-physiological bases. The efficacy of ESN, its ability to preserve donor nerve function, the necessity of disrupting the nerve connective sheaths of the donor nerve, the mechanism of reinnervation of the recipient nerve, and even the definition of the procedure have indeed all been questioned [27].

Are the nerve connective sheaths a barrier?

Epineurium

The epineurium is the outer connective sheath of the nerve, being areolar between the fascicles and more condensed around the nerve trunk. It is formed by bundles of collagen fibres, 60–100 nm in diameter, mostly

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aligned longitudinally. The largest nerve vessels, lymphatics and nervi nervorum are in this sheath [12, 29].

In an experimental model of end-to-side nerve connection, using fibrin glue, Bertelli et al. [5] attached the cut end of a recipient nerve against the intact epineurium of a donor nerve. No functional motor or sensory recovery was obtained with such a model. Considering that fibrin glue is effectively used in end-to-end nerve coaptation [28], the epineurium should be considered a barrier to reinnervation.

A certain amount of reinnervation of the recipient nerve has been demonstrated in ESN when an epineurial window is created in the donor nerve at the level of the connection site. To improve the results of ESN, some Authors [24, 38] have indeed suggested the creation of a large epineurial window in the donor nerve.

Perineurium

The perineurium is a dense connective sheath, 1.3–100 μm thick, which surrounds the fascicles. It is composed of three concentric layers: 1) internal: a layer of flattened perineurial cells with tight junctions; 2) intermediate: 3–15 concentric lamellae of flattened perineurial cells with long processes and basement membrane fusion, interdispersed with packed collagen fibers, 40–65 nm in diameter, mostly longitudinal, forming a double, spiral compact network; 3) external: a layer of gradual transition from perineurium to epineurium with thicker collagen fibres, perineurial cells interdispersed and replaced by epineurium fibroblasts [29].

Although initial studies did not document any difference between end-to-side connections, with or without a perineural window in the donor nerve [33, 41], subsequent studies suggested that a perineurial window is a prerequisite for effective nerve regeneration into the recipient nerve. Walker et al. [36] reported that a large (5 mm) perineurial window induced greater collateral sprouting or regenerative response than a small (1 mm) perineurial window, apparently without increasing cross sectional nerve injury or delaying functional recovery. Different Authors [3, 22, 39] reported a clear difference in the ultrastructural analysis of the site of nerve connection according to the presence or absence of an epi-perineurial window in the donor nerve. Regenerating axons in the recipient nerve were indeed seen only when an epi-perineurial window was performed in the donor nerve [3, 22].

Comparing epineurial and perineurial sutures, a significant increase in axonal regeneration was seen when perineurial sutures were used [3].

Endoneurium

The endoneurium is composed of fibroblasts and collagen fibres arranged mostly longitudinally, closely packed around axons and Schwann cells [29].

After making a simple perineural window in the donor nerve, regenerated axons in the recipient nerve were significantly fewer than after using a perineural window plus interruption of a number of axons, within their endoneurial tubes, in the donor nerve. Furthermore, the greater the number of axons injured in the donor nerve, the greater the axon regeneration response in the recipient nerve [22].

What type of axons regenerate?

After both experimental and clinical ESN [11, 15, 17, 19, 26, 30, 35], many Authors reported that sensory axon regeneration occurred alone or with significantly minor motor axon regeneration. Lutz et al. [17] reported that after ESN with a perineurial window, functional motor recovery was on average 70%, as compared to end-to-end neurorrhaphy, but satisfying functional results were unpredictable. When ESN was compared to end-to-end neurorrhaphy [16], the latter showed the best functional motor recovery.

When an axon count was performed after peroneal-tibial nerve ESN in the rabbit model, the number of regenerated axons appeared too low to permit any functional recovery [13].

What is the origin of regenerated axons in the recipient nerve?

Viterbo et al. [34] defined ESN as the connection of the cut end distal stump of the transected nerve (the peroneal) to an epineurial window opened on the side of an intact regional nerve (the tibial) in a rat model. This model, which is the most common in the literature, raised the possibility that regenerated axons could be provided by the proximal stump of the transected nerve, a phenomenon described as “invasion” or “contamination” [2] (Fig. 1A) and demonstrated by McCallister et al. [20]. To prevent such contamination, the proximal stump of the transected nerve has to be either directed away from the anastomosis site or sealed; the end-to-side coaptation site must also be sealed. Collateral sprouting of motor end units from other intramuscular nerves or cross innervation of the target muscle may be other possible sources of muscle reinnervation after ESN [26].