

Current concepts in end-to-side neurorrhaphy

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Abstract

In peripheral nerve injury, end-to-side neurorrhaphy involves coaptation of the distal stump of a transected nerve to the trunk of an adjacent donor nerve. It has been proposed as an alternative technique when the proximal stump of an injured nerve is unavailable or the nerve gap is too long to be bridged by a nerve graft. Experimental and clinical data suggests that end-to-side neurorrhaphy can provide satisfactory functional recovery for the recipient nerve, without any deterioration of the donor nerve function. The most accepted mechanism of nerve regeneration following end-to-side neurorrhaphy is collateral sprouting. The source of the regenerating axons traveling in the epineurium of the donor nerve is thought to be the proximal Ranvier's nodes at the site of end-to-side neurorrhaphy, however, histologic evidence is still lacking. Partial neurotomy of the donor nerve may enhance regeneration of motor neurons through end-to-side neurorrhaphy and reinnervation of motor targets.

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INTRODUCTION

Autologous nerve grafting remains the gold standard for the management of nerve gaps following peripheral nerve injury. Use of autologous nerve grafts is bounded by the limited amount of available tissue and the increased donor site morbidity. Several surgical alternatives have been reported with various success. These include the combination of nerve grafts and silicon tubes^[1], the use of synthetic or biologic nerve conduits^[2], tubes containing blood vessels^[3], the application of cultured Schwann cells^[4] and end-to-side neurorrhaphy.

It was not until 1992, when Viterbo *et al*^[5] reintroduced end-to-side neurorrhaphy, an almost forgotten technique of nerve coaptation. End-to-side neurorrhaphy involves coaptation of the distal stump of a transected nerve to the trunk of an adjacent donor nerve. It has been proposed as an alternative technique in cases of peripheral nerve injury, when the proximal stump of an injured nerve is unavailable or obliterated or the nerve gap is too long to be bridged by a nerve graft^[6-8].

End-to-side neurorrhaphy was first described by Letievant in 1873 as a reconstructive strategy of peripheral nerves in cases of large substance loss^[9]. The pioneer's

s idea was abandoned due to poor results that can be attributed to the use of conventional surgical instruments and non-microsurgical techniques without the use of a microscope. Almost nine decades later, many investigators have again experimented using this interesting technique^[5,10-15]. The results this time were very promising and since then, many studies have been performed resulting in improvement of functional results and further understanding of nerve regeneration after end-to-side neurorrhaphy.

COLLATERAL SPROUTING

The most accepted mechanism of nerve regeneration following end-to-side neurorrhaphy is collateral sprouting, where regenerated axons emerge from the most proximal Ranvier's node of the donor nerve to the coaptation site and travel in the epineurium of the donor nerve^[16-25]. Before axonal development, schwann cells are organized into columns at the coaptation site^[26]. At a later stage, these cells invade the epineurial layer of the recipient nerve. This is considered the critical step for the initiation of collateral axonal sprouting from the intact axons. It is supported that axons emerge from the Ranvier's nodes of the donor nerve proximal to the coaptation site^[25,27-29]. According to one study, Schwann cells were found to stimulate axonal regeneration from both the distal nerve stump and Ranvier's nodes of the donor nerve^[30].

The mechanism causing collateral sprouting after end-to-side neurorrhaphy may result from switching signals and/or switching factors, presumably neurotrophic^[19]. Zhang *et al*^[19] suggested that factors released from the Schwann cells, which have migrated to the epineurium, are transferred into the perineurium by diffusion and promote collateral sprouting from the closest to the injury site to Ranvier's nodes of the donor nerve.

It is well known that Neurotrophine-3 (NT-3) plays a distinct role in the processes of nerve regeneration and muscle reinnervation^[25]. NT-3 and its receptor Trk C are expressed in the coaptation site following end-to-side neurorrhaphy^[31]. Growth-associated protein-43 (GAP-43), a marker of growth cone formation, brain-derived neurotrophic factor (BDNF) and Trk B (BDNF receptor) are also detected in the coaptation site in lower concentrations and after NT-3 expression^[31]. In an end-to-side neurorrhaphy model using anti-GAP-43 antibody, growth cone direction was recorded from the donor nerve to the peripheral nerve segment of the injured nerve.

Many investigators have also shown the distinct role of nerve growth factor (NGF) during collateral sprouting^[32-37]. NGF is produced in end-organs following nerve injury. The secreted NGF is taken up by the axon terminals and transported retrogradely to the nerve cell body stimulating a secondary response. It has been shown that the combination of NGF and ciliary neurotrophic factor (CNTF) promotes axonal regeneration after end-to-side neurorrhaphy^[38].

FACTORS AFFECTING MOTOR REGENERATION

Biological responses of the donor neuron to factors emanating from the transected nerve have been implicated in the initiation of collateral sprouting for both sensory and motor axons. According to previous studies, significant motor functional recovery after end-to-side neurorrhaphy can be achieved without donor nerve axotomy^[39,40]. However, more recent studies suggest that donor nerve injury, such as axotomy or suturing, is required for motor reinnervation of the recipient nerve^[41,42].

Bontioti *et al*^[41] revealed increased expression of activating transcription factor 3 (ATF3), a marker of cell activation induced in sensory and motor neurons following peripheral nerve injury, after the creation of an epineurial window and/or suturing. According to these findings, an operative injury to the donor nerve during end-to-side neurorrhaphy is the main prerequisite for axonal sprouting.

A dose-response relationship between axotomy of the donor nerve and motor axons regeneration has been demonstrated^[42]. Presumably, motor fibers from the donor nerve may enter the recipient nerve segment to supply muscles which were normally innervated by motor fibers from the recipient nerve^[43].

DOUBLE END-TO-SIDE NEURORRHAPHY

Viterbo *et al*^[13] first described double end-to-side neurorrhaphy. In this technique, both proximal and distal stumps of the recipient nerve are coapted in an end-to-side fashion to the trunk of an adjacent donor nerve (Figure 1). The regenerated axons use the epineurium of the donor nerve as a bridge to find the distal stump. It has been suggested that this technique stimulates axonal growth by a supercharged effect compared with end-to-end repair. Interestingly, when double end-to-side neurorrhaphy was compared with the conventional end-to-side technique, the recipient nerve following the double terminolateral technique was found to contain a significantly larger number of myelinated nerve fibers distal to the neurorrhaphy site^[44]. Two sources of axons may contribute to the increased number of regenerating nerve fibers, axons sprouted collaterally from myelinated nerve fibers at the node of Ranvier of the donor nerve, and axons that arise from the proximally coapted nerve segment.

Our experimental knowledge of double end-to-side neurorrhaphy, leads us to the belief that double end-to-side coaptation may be a valuable tool when the classic end-to-end technique is not possible. In our previous studies in rats, functional evaluation and axonal counting data demonstrated that nerve regeneration can be supported using the intact nerve bridge technique for a distance of 1.2 cm in a rat sciatic model^[44].

Epineurial vs perineurial window

A technical parameter that may significantly affect axonal

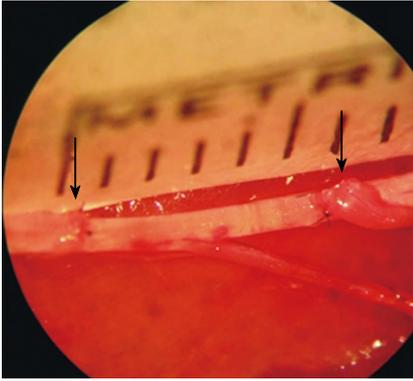


Figure 1 Double end-to-side neurorrhaphy with 0.6-cm regeneration distance between the proximal and distal stump of the recipient nerve (black arrows). In both neurorrhaphies, coaptation was performed with 3 interrupted 9-0 nylon sutures placed at 120°.

regeneration after end-to-side neurorrhaphy involves the application of epineurotomy or perineurotomy. Viterbo^[5] and Cao^[16] demonstrated no significant difference for end-to-side neurorrhaphy with and without epineurial window. Likewise, Viterbo *et al*^[43] revealed no difference between neurorrhaphies with and without perineurial window. These observations may, in part, be explained by the finding that the regenerating axons following end-to-side neurorrhaphy can penetrate the endoneurium, perineurium, and epineurium^[17].

According to some investigators, histologic results were better when a perineurial window was opened^[19,20]. This can be attributed to the greater degree of axonal damage to the donor nerve and subsequently the enhanced axonal regeneration after perineurotomy. When fibrin glue is used as an alternative to end-to-side neurorrhaphy, no damage to the donor nerve trunk is produced. This may explain the absence of muscle reinnervation after end-to-side coaptation with fibrin glue, without removing the epineurium^[46]. According to our studies, resection of a small part of the epineurium and placement of epineurial sutures without damaging the underlying perineurium improves the functional outcomes following terminolateral nerve repair without compromising the function of the donor nerve (Figure 2)^[44].

Clinical applications

To date, there have been no large clinical series describing either satisfactory or disappointing results after end-to-side neurorrhaphy. In 1993, Viterbo^[11] first applied end-to-side neurorrhaphy in recent clinical practice with the use of cross-facial nerve graft transplantation for the treatment of facial palsy. Reinnervation was observed in selected patients. A few years later, end-to-side neurorrhaphy was used to bridge the nerve gap after ulnar nerve injury. In this case, the median nerve was the donor nerve^[47]. The authors reported ulnar nerve motor and sensory restoration without deterioration of the donor nerve. Yüksel *et al*^[48] described a case of severe upper extremity nerve injury treated with end-to-side neurorrhaphy



Figure 2 End-to-side neurorrhaphy between the tibial nerve (double asterisk) and the peripheral stump of the peroneal nerve (single asterisk) 90 days after surgery. Note the smooth transition from one trunk to the other resembling normal bifurcation of the tibial nerve. Also note the newly formed vessels at the outer layer of the nerve trunks traveling from the donor tibial nerve to the recipient peroneal nerve.

phy of the median and radial nerves to the ulnar nerve. The patient had satisfactory sensory recovery.

Amr *et al*^[49] reported satisfactory results in 11 cases of brachial palsy injury treated with end-to-side and side-to-side grafting neurorrhaphy. Deterioration in donor muscle motor power was observed in one case, which improved a year later. Santamaria *et al*^[50] sutured the lateral antebrachial cutaneous nerve in an end-to-side fashion to the cervical plexus, posterior auricular, or hypoglossal nerve where it was not possible to preserve the proximal stump of the lingual nerve in twenty-eight patients with tongue cancer who underwent hemiglossectomy and primary reconstruction with innervated radial forearm flaps. Sensory tests were significantly diminished when end-to-side nerve repair was used.

In digital nerve reconstruction, of 5 patients who underwent end-to-side neurorrhaphy four had sensitivity near to completely normal and one patient had a poor result^[51]. Satisfactory results in all patients were also obtained in a series of ten nerve defects at the palm or digit level treated by end-to-side neurorrhaphy. Donor nerve injury was recorded in one case^[52].

CONCLUSION

Experimental and clinical studies suggest that end-to-side neurorrhaphy can provide satisfactory functional recovery in the recipient nerve, without any deterioration of donor nerve function. The source of the regenerating axons traveling in the epineurium of the donor nerve is thought to be the proximal Ranvier's nodes at the site of end-to-side neurorrhaphy, however, histologic evidence is still lacking. Partial neurotomy of the donor nerve may enhance regeneration of motor neurons through end-to-side neurorrhaphy and reinnervation of motor targets. To date, a limited number of reported cases in clinical practice have revealed that the end-to-side technique may become a viable means of repairing peripheral nerves in certain clinical situations.

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