Connector-Assisted Coaptation for Repair of Short Gaps in Transected Nerves

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Abstract

Many factors that affect nerve repair outcomes when addressing nerve coaptation are beyond the surgeon's control. Following resection to healthy tissue, there are six critical and controllable factors that may optimize functional outcomes when addressing the coaptation of the nerve end. These include: 1) reducing tension at the coaptation site, 2) minimizing suture irritation within the coaptation, 3) macroscopically re-aligning nerves, 4) providing a microscopic environment conducive to neurotropism, 5) ensuring a mechanically stable repair, and 6) isolating the nerve coaptation site. Transected nerves with short gaps may be repaired by direct suture repair or connector-assisted coaptation. Clinical publications from Lundborg, Weber and Boeckstyns have demonstrated that connector-assisted coaptations provide outcomes that are equivalent to or better than direct suture repair when the gap length is < 5mm. Additionally, the repair site and ultimate outcome may be affected by the composition of the coaptation aid. Ideally, nerve repair implants are biocompatible, protect the repair site, and work in conjunction with the body's natural healing process.[1] This paper reviews the options for short gap peripheral nerve repair, factors that influence regeneration at the coaptation site, the benefits of connector-assisted coaptation in nerve repair, and considerations for selection of implants for use in connector-assisted coaptation. Additionally, the benefits of AxoGuard® Nerve Connector for connector-assisted coaptation are discussed.

Introduction

Peripheral nerve repair can be very rewarding for both surgeon and patient when patient outcomes are optimized. In many cases, however, the results are less than optimal. In theory, tension-free suturing to re-approximate the transected nerve ends, the historical standard, should provide the best possible opportunity for success. This technique provides alignment of the nerve structures allowing vascular, axonal and cellular outgrowth to traverse the coaptation gap. Unfortunately, published clinical outcomes for this technique have been disappointing with many studies reporting satisfactory outcomes ranging from 10% to roughly 80% of the subjects, many averaging no better than 50%.[2-4]

Many factors can affect the outcomes of suture repair. Assuming the damaged tissue is resected back to healthy tissue, the unanticipated tension on the nerve appears to be the biggest culprit. By forcing misalignment, impairing vascularity and impeding axonal regeneration, tension at the coaptation site can adversely affect many of the biological processes essential to nerve healing.[5-7] Tension at the coaptation site is difficult to visualize and quantify. However, tension should be assumed present in the repair site, unless nerve laxity is evident. Also detrimental to regeneration is fascicular mismatch, suture irritation, inflammatory in-growth and axonal escape.[2]

The concept of entubulation of the nerve ends is not a new one; Gluck first introduced it in the 1880's. Of interest however is the prevailing thought that a tube placed over the transected nerve ends is an alternative to nerve autografting. This is actually counterintuitive to the early work that popularized this concept.[8-10] Tube repairs were originally developed and shown to have clinical utility as an aid to the coaptation process, not as a replacement for nerve grafts. The tube repair provides a protected environment for the nerve coaptation, relocates the sutures away from the coaptation face and out of the way of the regenerating nerve, transfers the tension loaded across the nerve away from the coaptation and provides an area for selective reinnervation of the distal tissues. The merit of this technique has been examined in several clinical studies,[8,10-11] each demonstrating the benefits of a connector-assisted coaptation over traditional suture. This paper discusses the potential benefits and limitations of a connector-assisted coaptation with AxoGuard® Nerve Connector.

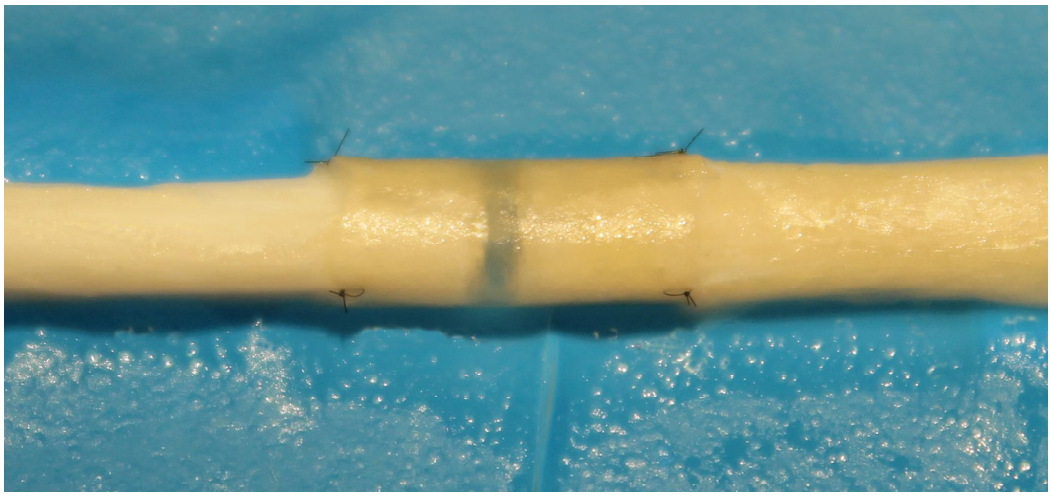

Figure 1: AxoGuard® Nerve Connector-assisted coaptation.

Repair Options for Short Nerve Gaps

A severed peripheral nerve presents a challenging repair for a surgeon attempting to restore a patient's sensory and motor function. Historically, transected peripheral nerves have been repaired directly with suture; however, direct repair should only be performed if the nerve coaptation face is healthy fascicular tissue rather than scar,[12] and if the coaptation face is truly tension-free after completion of the repair.[13] In many transections, regeneration may be optimized with the use of a nerve connector. Placement of a connector at the coaptation face allows for tension-free re-approximation of the nerve ends by minimizing the need to stretch the nerve stumps, which may have retracted due to normal physiologic tension across the nerve, in order to overcome the gap.[13] A connector-assisted coaptation may reduce the number of sutures required for nerve stump re-approximation and may allow suture placement away from the nerve coaptation site, thereby reducing the negative impact of sutures at the critical zone of regeneration.[10,14-15]

Implant Material Considerations

Another consideration in the repair approach is the material composition of the coaptation aid, which can affect the repair site, and therefore the repair outcome. An ideal material is biocompatible and works with the body's natural healing process while providing protection and allowing nutrient flow to the healing repair site.[1] AxoGuard® Nerve Connector is a coaptation aid used for tensionless repair of transected nerves that possesses many structural and material characteristics beneficial in repair of transected nerve with short gaps. It is the only porcine derived intact extracellular matrix (ECM) that is commercially available for nerve repair.

Benefits of Connector-Assisted Coaptation with AxoGuard® Nerve Connector

In short gap peripheral nerve repair, connector-assisted coaptation has been shown to:

- Alleviate risk of tension and tension-induced ischemia and associated regeneration failure[13] in the repaired nerve.
- Provide a physical barrier from surrounding tissues which allows neurotropism to occur across a small gap.[1,16]
- Protect the coaptation site from mechanical damage and infiltration of fibrotic tissue.[1,16]
- Provide a semi-permeable protective environment which allows diffusion of nutrients.[1,5,17]
- Revascularize as a new soft tissue layer is formed.[18-20]
- Potentially reduce surgical time up to 40% percent compared to direct suture repair.[11]
- Provide desirable handling properties including conformability, suturability, and visualization of the coaptation.

Nerve Repair and Regeneration with a Nerve Connector

Nerve connectors have been used successfully for years to bridge very short gaps. Studies have shown that in short nerve gaps (< 5mm), a cable made from fibrin, fibrinogen, and fibronectin forms across the gap.[16,21] This provisional cable is then populated by erythrocytes, macrophages, and polymorphonuclear leukocytes (Figure 2).[21] Fibroblasts and Schwann cells then infiltrate the resulting cellularized cable. The Schwann cells deposit collagen and form Bands of Büngner (oriented laminin columns with surrounding aligned Schwann cells).[16,22] Regenerating nerve fibers enter the gap and follow the Bands of Büngner to reach the distal nerve stump leading to reinnervation of the target organ.[22-23] The newly deposited connective tissues are then remodeled into a site-appropriate regenerated tissue.[23-24] AxoGuard® Nerve Connector, which is composed of small intestine submucosa, remodels to become a permanent protective layer of epineurium-like tissue. [23]

Figure 2: Regeneration within AxoGuard® Nerve Connector with a gap < 5mm. A) The Connector fills with fibrin and the milieu from the nerve ends. B) Revascularization of Connector and fibrin cable begins. Schwann cells migrate into the fibrin bridge and form Bands of Büngner to support regenerating axons. C) With the nerve continuity restored, the newly remodeled Connector becomes a permanent protective layer of epineurium-like tissue.

Limitations of Hollow Tube Nerve Repair

Consideration needs to be given to the size of the nerve gap and the local tissue environment as each of these factors affects the quality of the fibrin cable formation. If the cable does not form or the gap is too large for a robust cable to form, regeneration will be hindered.[24] In a clinical study by Weber et al., in gaps < 5mm, a tube repair reliably provided good to excellent recovery,[10] while in other published studies, 30-40% of the subjects had fair to poor outcomes when the nerve gap was > 5mm.[10,25-27] Boeckstyns et al. published similar results in 2013 for mixed nerve repairs stating that a hollow tube should not be used when the nerve gap is greater than 6mm.[11]

Local Tissue Environment

The local tissue environment may affect the quality of nerve regeneration when suture is used to coapt the nerve stumps. Non-resorbable suture is generally used to connect nerve stumps, coaptation aids, and nerve grafts. These non-resorbable sutures may be made from nylon or polypropylene, both of which may cause local inflammatory reactions. These reactions range from minor (small, compact fibrous tissue layer encasing the suture) to severe (formation of granulomas and fibrous tissue encapsulation).[14-15] The presence of inflammation at the coaptation face (i.e., the site of axonal regeneration) negatively impacts nerve regeneration.[28]

The use of a nerve coaptation aid effectively relocates the sutures away from the coaptation face and away from the growth cones of regenerating axons. In animal studies, nerve repairs using a coaptation aid exhibited better functional outcomes when compared to directly sutured nerve repairs.[28-29] Additionally, nerves repaired using a coaptation aid showed superior myelinated fiber population and diameter, and better functional recovery in an animal model.[28] The use of a coaptation aid to re-approximate nerve stumps may provide various benefits during nerve regeneration, including displacing sutures off the coaptation face.

Use of a Nerve Connector to Alleviate Tension at the Repair Site

It is important to minimize tension in nerve repair to optimize outcomes as even small amounts of tension can lead to poor results. A repair site under tension may result in decreased blood flow leading to ischemia, as well as fascicular distortion and axonal misdirection.[13,30] Increased tension at the coaptation site may ultimately lead to an increase in endoneurial collagenous connective tissue formation (i.e., scar tissue) and decreased neural angiogenesis within the repair segment.[30] Tension at the repair site has also been associated with decreased axonal outgrowth and sub-optimal outcomes (Figure 3).[31] The negative effects of suturing under tension are even more dramatic if the nerve stumps are scarred from a previous injury.[17] Because of the negative impact of tension on nerve regeneration, tension-free repair is essential for optimal functional outcomes.

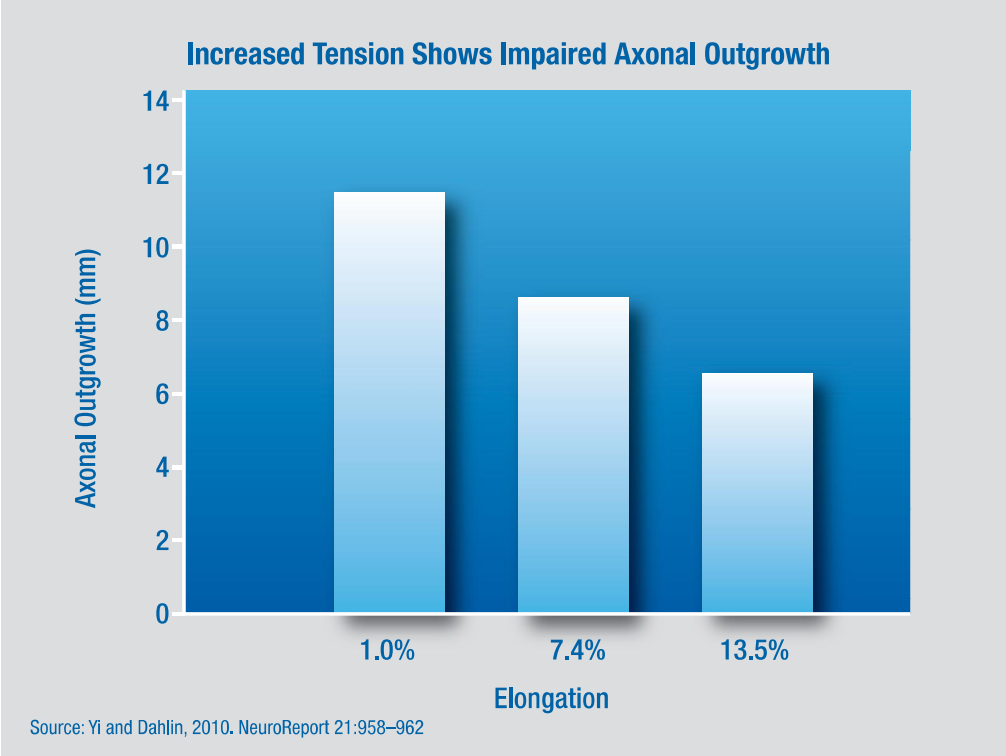

Figure 3: Bar graph representing change in tension and the associated impact on axonal outgrowth.[31]

Resection Increases Tension at the Repair Site

Peripheral nerves are viscoelastic structures that, when transected, undergo elastic retraction resulting in increased gap length compared to the original defect.[16,32] Compounding this retraction is the loss of tissue due to the injury itself and to the resection required to trim back the nerve stumps to healthy fascicular structures. After proper preparation of the nerve, it is rare to have no gap present between the nerve ends. Since axons cannot regenerate across scarred tissue, loss of nerve tissue due to injury or resection effectively increases the gap length between the stumps.

Repair Site Tension is Hard to Measure

When the nerve stumps are re-approximated by end-to-end suturing, it is difficult to estimate the amount of tension present at the repair site. While traditional means for assessing tension such as visual cues, tactile feel and suture pull-out are useful, they lack the sensitivity to detect the critical threshold of tension, potentially misleading the surgeon to assume the repair is tension-free.[33] Unlike an intact, uninjured nerve which has tension evenly distributed along its length, the distribution of tension in a transected nerve becomes disproportionally concentrated at the sutured repair site.[30]

Tension-free repair may be achieved using various techniques such as direct repair with mobilization, connector-assisted coaptation, nerve grafting with on-site harvested nerve autograft, or nerve grafting with off-the-shelf nerve allograft. Joint immobilization as a means of alleviating tension in a repaired nerve may be insufficient, especially in the presence of a concomitant tendon repair that relies on mobility for proper healing. Surgeons may use external neurolysis and mobilization to bring nerve stumps in close proximity.[13] Mobilizing the nerve often requires tissue dissection, which may disrupt vital blood supply to the nerve. Nerve stumps may be mobilized over several centimeters of stump length without detrimental effects; however, damage to the vascular supply during mobilization may lead to impaired regeneration.[34-35] Mobilization beyond 24% of the total nerve length results in compromised vascular supply to the repair site and impaired regeneration (i.e., ischemic degeneration).[35]

Measurements of tension are frequently based on the percent elongation of the nerve. Based on animal studies, re-approximation of transected nerve stumps is recommended only if nerve elongation is limited to 10% of the total length of the mobilized nerve stumps, after which the microvascular flow is reduced by 50%, leading to ischemia.[32,36] Nerve elongation of as little as 15% can further reduce blood flow by as much as 80%, resulting in irreversible ischemic damage and impaired nerve growth.[32] Yi and colleagues found that with only 7.4% elongation of the nerve stumps, axonal extension was reduced by 29% while increased elongation to 13.5% resulted in a 48% reduction in axonal extension (Figure 3).[31]

A simple equation quantifies stretching in mobilized nerve stumps by comparing the ratio of the gap to the ratio of the nerve freed from the tissue bed:[6]

$$\left(\frac{\text{Gap Length}}{\text{Proximal Stump Length + Distal Stump Length}} \right) \text{x } 100 = \text{\% Elongation}$$

This equation takes into account the amount of nerve mobilized and the percent elongation to determine whether blood flow will be impacted after repair. For example, to limit elongation to no more than 5%, a nerve gap of 5mm would require a total of 100mm of nerve stump mobilization to achieve tension-free direct suture repair. However, 100mm of nerve stump exceeds the amount of mobilization recommended to avoid damage to the vascular supply and resulting impaired regeneration.[35]

Connector-assisted coaptation minimizes the need to mobilize the injured nerve from its surrounding tissue bed. *In vivo* studies have shown that alleviating tension at the repair site through use of a coaptation aid may result in improved neural angiogenesis and better functional nerve recovery.[30]

Nerve Connector Aids Alignment and Supports Neurotropism

Maintaining a small gap (< 5mm) between nerve stumps within a connector allows axons to find their own way to their targets and may be more beneficial than a directly sutured forced misalignment.[37] Use of a connector allows for re-approximation with a small gap (≤ 5mm) left between proximal and distal stumps. The connector also acts as a containment device for nutritive milieu, which consists of neurotropic factors and other growth factors. Evans et al. studied the beneficial effects of connector-assisted coaptation in a rodent mixed nerve model.[37] They theorized that the chemotactic effects of elements within the milieu helped to guide sensory axons to sensory targets and motor axons to motor targets.[37] These findings demonstrated that a connector-assisted coaptation provided superior results in the studied model to a directly sutured nerve with a forced misalignment, regardless of the alignment of the nerve stumps within the connector. These beneficial effects could be realized in a connector-assisted repair, especially when the internal topography of the injured nerve stumps is not self-evident.

Nerve Connector Isolates and Protects the Nerve Repair Site

Protection of a peripheral nerve repair site has been practiced since the 19th century and continues today in an effort to minimize scar ingrowth, reduce axonal outgrowth, longitudinally align regenerating axons and provide mechanical support to ensure a stable repair site (Figure 2). Nerve fascicles are surrounded by perineurium, which serves as the blood/nerve barrier to isolate them from surrounding tissues. When a nerve is traumatically injured, the perineurium is compromised which results in increased permeability of endoneurial vessels and exudation of circulating proteins followed by spreading of protein within the endoneurium.[17,38] Studies have shown that post-transection deterioration of the blood/nerve barrier can endure for up to 6 months allowing non-nerve cells to enter the peripheral nerve.[17] Previous experiments have shown that incremental improvements are possible after protecting nerve repairs with a non-reactive, biodegradable membrane.[16] The surgical entubulation and re-approximation of proximal and distal nerve stumps via a nerve connector allows for repair site stability, macro alignment, relief of tension and protection of the regenerating peripheral nerve during healing (Figure 1).

Nerve Connector May Reduce Operative Time

Recent clinical studies have found that a connector-assisted coaptation can reduce the surgical repair time by 40% over traditional epineurial sutures.[11] Connectors can be particularly useful in smaller multi-fascicular nerves, where proper fascicular alignment and opposition are difficult.[17] A connector-assisted coaptation may reduce the likelihood of axonal wasting, collateral sprouting, and fiber misalignment.[17] Connectors may provide a protective barrier for the regenerating nerve,[21] and can also serve as a containment reservoir for cells, growth factors, and nutrients that extrude from injured nerve stumps.[1] Each of these factors plays a role in nerve healing and, ultimately, functional outcomes. Clinical publications from Lundborg, Weber and Boeckstyns have demonstrated that connector-assisted coaptations provide outcomes that are equivalent to or better than direct suture repair when the gap length is under 5mm.[14-15,22]

Considerations for Selection of Implant

Although there are a number of commercially available hollow tubes and connectors for repair of injured peripheral nerves, not all have the same characteristics. These implants have been made from a variety of materials including autologous tissues, non-resorbable synthetic materials, resorbable synthetic materials, and resorbable biological materials.[1,23] It is important to understand the material properties of the various implants and how each works with the body in order to achieve the best possible outcome. Research on various material characteristics including geometry, micropore size and orientation, and mechanical properties has yielded ideal material properties for nerve connectors.[23] Implants used for peripheral nerve repair should meet the following criteria for optimal performance: 1) biocompatible without provoking an undue inflammatory response, 2) biodegradable while maintaining biomechanical integrity during regeneration, 3) permeable to allow diffusion of oxygen and nutrients while preventing fibrous tissue ingrowth into the repair site, and 4) soft and flexible for easy handling.[1]

Biocompatibility and Implant Fate

Implanting a non-resorbable material can lead to a foreign body reaction and negative effects on peripheral nerve regeneration.[18] Such reactions led to the development of resorbable materials such as degradable synthetic materials, reconstituted type I collagen, and decellularized extracellular matrices (ECMs).[1] Decellularized ECMs contain natural components found in the origin tissue while cells that may trigger an undue inflammatory response have been removed.[20]

Regenerating neurites (projections of a neuron) utilize specific interactions with extracellular matrix proteins for adhesion to biologically derived scaffolds.[23] Specifically, ECM proteins, including laminin, collagen, fibronectin, proteoglycans, and integrin mediate specific receptor-ligand interactions during healing.[23] Implants containing the basal lamina (laminin and fibronectin) are also known to support axonal regeneration across gaps.[17] Various isolated ECM components have been artificially integrated into scaffolds to promote axon growth;[23] however, decellularized ECMs such as small intestinal submucosa (SIS), the source material for AxoGuard® Nerve Connector, may contain many of these endogenous components.[20] The ECM components of AxoGuard® Nerve Connector have been extensively studied and contain many of the proteins that are associated with neurite growth including collagen,[39] hyaluronic acid, heparin, heparan sulfate, chondroitin sulfate A, dermatin sulfate,[40] fibronectin, laminin, and entactin.[41] Studies have shown that, compared to control media, media conditioned with SIS resulted in PC12 cells (commonly used as a model for sympathetic neurons *in vitro*) expressing neurite-like extensions and fibroblasts to secrete vascular endothelial growth factor,[41] both indicators of a regenerative response.

Permeability

The use of a semi-permeable tube in peripheral nerve repair allows for diffusion of oxygen, nutrients, and vascular ingrowth, with a desirable pore size ranging from 5-30µm.[1,17,23] Such semi-permeable tubes have shown improved regenerative capacity.[17] The porosity of minimally processed SIS (20-30 µm),[42] the source material for AxoGuard® Nerve Connector, falls within this pore size range making it excellent implant for use in peripheral nerve repair.

Handling

Implant handling properties also play an important role in the utility of a nerve connector. An ideal product will retain its shape to allow for easy insertion of the nerve stumps, be strong enough to hold suture, and flexible to allow conformity to the nerve.[1] Further, a semi-transparent tube allows for visualization of the nerve stumps within the tube and may allow for more accurate positioning of the fascicles to achieve proper alignment. All of these desired handling attributes are characteristics of AxoGuard® Nerve Connector.

Conclusion

Many factors that affect nerve repair outcomes when addressing nerve coaptation are beyond the surgeon's control. Following resection to healthy tissue, there are six critical and controllable factors that may optimize functional outcomes when addressing the coaptation of the nerve end. These include: 1) reducing tension at the coaptation site, 2) minimizing suture irritation within the coaptation, 3) macroscopically re-aligning nerves, 4) providing a microscopic environment conducive to neurotropism, 5) ensuring a mechanically stable repair, and 6) isolating the nerve coaptation site.

AxoGuard® Nerve Connector is the only commercially available nerve connector composed of intact extracellular matrix which provides the desired structural, material and handling characteristics for a peripheral nerve repair implant for short nerve gaps (< 5mm). AxoGuard® Nerve Connector may be implanted to alleviate tension at the coaptation site and help maintain blood flow in the nerve stumps. The use of AxoGuard® Nerve Connector may augment nerve regeneration by providing a hospitable wound healing environment while forming a vascularized soft tissue layer around the nerve. AxoGuard® Nerve Connector is an extracellular matrix that consists of both a collagen scaffold and non-collagenous components that are utilized in the wound healing cascade. AxoGuard® Nerve Connector has been shown to maintain permeability to allow the flow of oxygen and nutrients necessary for axonal regeneration. Its semi-translucent nature allows for visualization of the nerve stumps within the Connector and easy visualization for suture placement. AxoGuard® Nerve Connectors are strong, flexible, easily sutured, and stored at ambient temperature. The combination of ease-of-use, shelf-storage, and beneficial material properties make AxoGuard® Nerve Connector a viable and attractive option for use as a nerve connector in short gap peripheral nerve repairs (Figure 4).

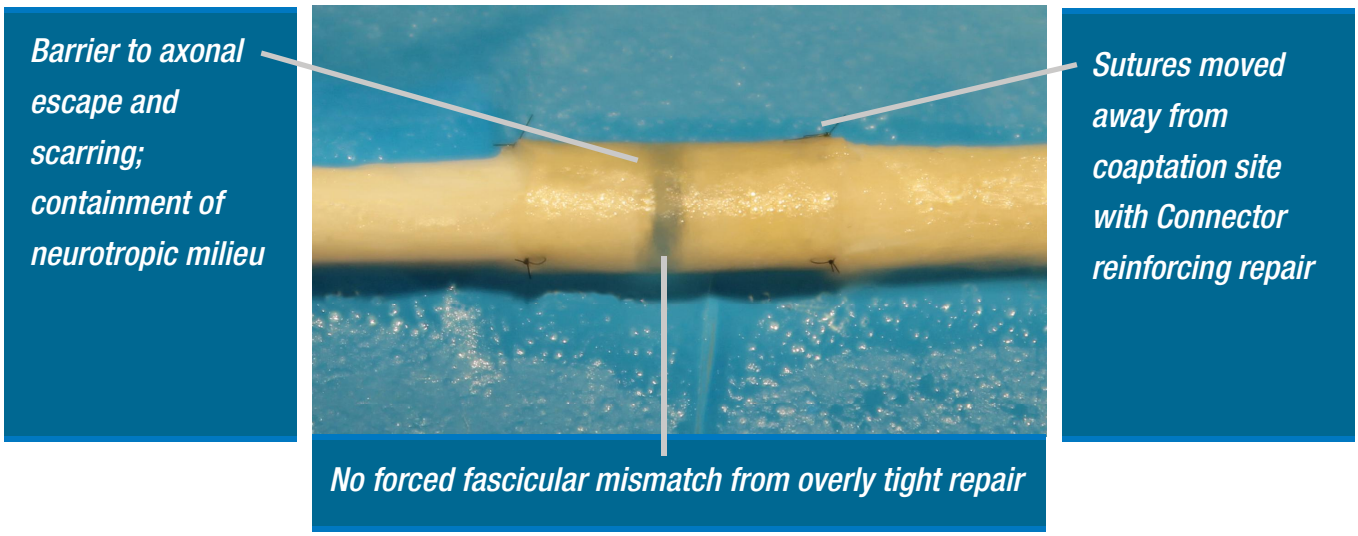

Figure 4: Benefits of AxoGuard® Nerve Connector-assisted coaptation.

Indications for Use

AxoGuard® Nerve Connector is intended for the repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity. The device is supplied sterile and is intended for one-time use. Indications for Use may vary by country, please see package inserts for specific indications.

Contraindications

AxoGuard® Nerve Connector is derived from a porcine source and should not be used for patients with known sensitivity to porcine material.

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AxoGuard® NerveConnector

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