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REVIEW ARTICLE

Mini-review: Bridging Nerve Gaps with Nerve Grafts or Nerve Conduits

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Introduction

The concepts of nerve repair and regeneration was described as early as 7th century by Paul of Aegina. In 1850, Augustus Waller made a fundamental contribution on the pathophysiology of nerve injury by describing anterograde myelin and axonal degeneration[1]. The first successful nerve regeneration after surgical repair was reported by Cruikshank in 1795. Primary epineurial suturing and nerve suturing techniques were described by Heuter (1871) and Mikulicz (1882) respectively[2]. Albert (1876) pioneered nerve grafting procedures to bridge nerve gaps. Nerve grafting is recommended whenever a direct repair is likely to result in excessive tension at the repair site[3]. In the past, nerve stretching, bone shortening, extremity positioning and stump mobilization were some of the procedures used to shorten the bridging gaps, most of which are now obsolete. In current clinical practice, the ideal choice to circumvent such a scenario is to use an autologous nerve graft. Tubulization techniques may be used for smaller gaps < 3cms, but larger defects require nerve grafts[4,5].

Anatomical and physiological considerations

Understanding the connective tissue layers and the fascicular anatomy of the nerve is essential before considering repairing an injured nerve. The nerve is enclosed in an external epineurial sheath, composed of connective tissue and longitudinal blood vessels. Within the nerve, an internal epineurium demarcates fascicles and group of fascicles. Each individual fascicle is surrounded by perineurium. The fascicles contain the axons, which are in close association with Schwann cells, both enclosed in endoneurium[6]. Based on the fascicular pattern, nerves can be divided into four basic types. Monofascicular indicates where the nerve contains only one fascicle, with digital nerve serving as the classical example. The sural nerve contains a few fascicles and is classified as an oligofascicular nerve. The fascicles in a polyfascicular nerve may be in a grouped or diffuse (ungrouped) pattern. Major nerves, like, median, radial, ulnar, tibial and common peroneal nerves are considered as polyfascicular nerves, with the fascicles often grouped, and the topography of the different motor and sensory nerve fibers within are reasonably well known. The proximal spinal nerve roots are also considered as polyfascicular nerve, however the fascicles are ungrouped with less defined perineurium[7]. The proportion of connective tissue within the nerve varies considerably, from 25%-85%. The perineurium is the source of main tensile strength to the nerve. Both epineurium and perineurium layers can take and hold sutures[8].

When nerve graft is deployed, commonly utilizing small sensory nerve (the sural nerve being the commonest donor nerve), the axons within the donor nerve will undergo Wallerian degeneration. The graft acts as a biological conduit for transmitting the regenerating axon from the healthy proximal nerve stump to the distal nerve stump. The nerve grafts, if of small caliber, will rapidly acquire vascularization from the surrounding connective tissue bed and thus maintain viability.

Once injured, peripheral nerves have the potential to regenerate and reinnervate end-organs, with good functional recovery[9] However, the possibility of spontaneous regeneration and resulting functional recovery are governed by the extent of nerve injury. As a practical rule, all *sharply* lacerated nerves with complete loss of function should be explored and repaired primarily without delay. Bluntly lacerated nerves (resulting from crush injuries) should be repaired after a period of 2-4 weeks. Patients with closed injuries, most commonly associated with long bones fractures or traction injury to the brachial plexus, are

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allowed a period of 3-4 months of conservative treatment before surgical exploration is advised[10]. This period of watchful waiting allows for the spontaneous recovery of the less severe nerve injuries in continuity so that these patients are appropriately excluded from an unnecessary nerve operation.

Surgical Principles and Techniques

Surgeons need to be prepared and aware of the anatomical variations, particularly when dealing with the brachial plexus anatomy. Short acting paralyzing agents are given at the induction of anesthesia to allow intra-operative nerve stimulation. Sharp dissection is performed and unnecessary manipulation is avoided as it may transform an incomplete injury into a complete one, or may disturb the normal fascicular orientation. The use of magnifying loupes can be useful in this part of the dissection. A very important principle, whenever possible, is to expose normal nerve proximal and distal to the injury and then approach the area of injury from either side. Both healthy proximal and distal ends of the injured nerve are found and encircled using Penrose drains or vessel loops for smaller nerves. In fresh lacerating injuries, the gap between both ends is usually small and needs only minimal edge refreshment and primary repair. Primary end-end repair can be aided by longitudinal mobilization of the nerves from surrounding tissue planes. For the repair itself, the use of microsurgical instruments is encouraged, such as jeweler's forceps and fine-tipped needle drivers for handling fine 8-0 and 9-0 monofilament nylon micro sutures. Fibrin glue (Tisseal, Baxter Healthcare) can be used to reinforce the repair. Beware that not all the commercially available surgical glues are suitable for peripheral nerves repair.

Most injuries however are in continuity, in which neuroma resection and graft repair is required. Once a neuroma-in-continuity is found, a circumferential dissection is carried out (external neurolysis) to free the neuroma from the surrounding tissue. Sensory nerve action potential (SNAP) recording are performed -if available. SNAP positive response generally indicates the presence of viable axons within the neuroma, in such situations external neurolysis is considered adequate and is associated with good functional recovery[11]. Absence of SNAP requires neuroma resection and graft repair. When SNAP monitoring is not available, a disposable nerve stimulator (Vari-stim® III) used at a current of 2 mA proximal to the neuroma may give useful information. The nerve stimulator used by anesthesia is readily available and multiple disposable needle lengths can be utilized for stimulation. The key here is to observe if stimulation proximal to the neuroma gives visible muscle contractions from muscles innervated by the nerve. If such is the case, the resection of the neuroma is not performed. In the case of negative SNAPs and/or lack of evoked muscle activation, the neuroma is prepared for resection Adequate resection of the neuroma is a critical step of the repair. Scarred proximal or distal nerve ends will prevent the growing axon from reaching the target muscles. The scarred proximal and distal ends are refreshed until a healthy non-scarred part of the nerve is reached on both sides. Both edges of the neuroma are often funneled and it is advisable to carry on the trimming till one reach the cylindrical part of the nerve. The healthy cut edge of the nerve is recognized when the endoneurium appears to "pout" or mushroom out of the fascicle (because of the positive endoneurial pressure). At this step, bleeding can be encountered from the epineurial or the perineurial vessels that can be controlled with gentle pressure, while a persistent bleeding can be controlled using small amounts of bipolar current via fine tipped forceps. The use of adequate magnification and micro-irrigator with saline are useful to precisely identify the bleeding points and minimizing nerve trauma produced by coagulation.

Once ready for repair, it is the surgeon's decision whether to use nerve autograft or tube repair. A most important factor for this decision is the length of the gap needed to bridge. The longer the gap (more than2 cm), the more appropriate the use of nerve autograft.

Nerve Autograft Repair

Grafting techniques using nerve autografts to bridge nerve gaps remain the gold standard in repairing nerve gaps produced by injury. Nerve grafting technique is preferred over direct primary suture technique when the gap between the proximal and the distal stumps is long, or when direct repair produces significant tension on the nerve repair site, as this tension is known to reduce the final functional recovery[4]. Before considering graft repair, the surgeon should make reasonable attempts to reduce the nerve gap to perform primary suture repair and avoid the usage of grafts (Fig 1). Generous mobilization of proximal and distal ends for considerable segment may allow the surgeon to gain 1-2 cm of length. Flexion of the elbow or the knee may shorten the distance and allow a primary

repair of the ulnar or the common peroneal nerve respectively. If the above maneuvers allow end-end repair without tension, then a graft repair is avoided. In all other circumstances, it is better to interpose a short nerve graft (or tube) to repair the gap (Fig 2).

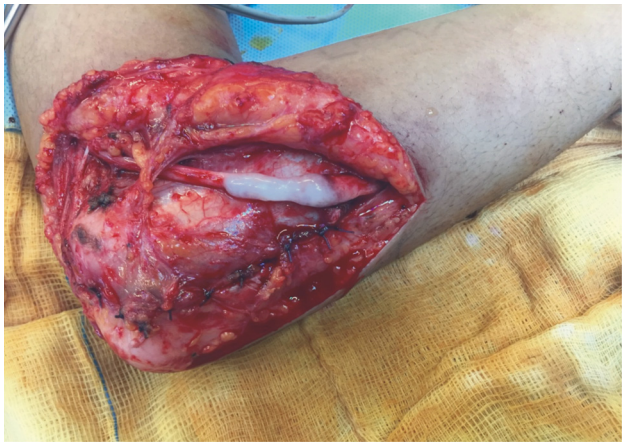

Fig. 1 Intra-operative photograph demonstrating transposition of the ulnar nerve anterior to the flexors muscle mass, aided by gentle elbow flexion to achieve primary repair bridging a 3 cm gap. The repair site was further augmented by glue. Note that glue is around the repair site only without adherence to the surrounding tissue.

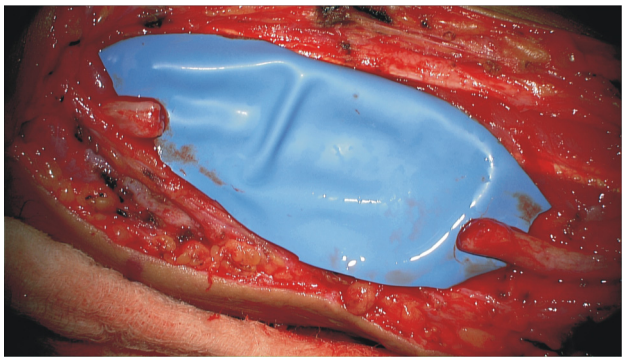

Fig. 2 (a) Following section of the neuroma to the healthy fascicles

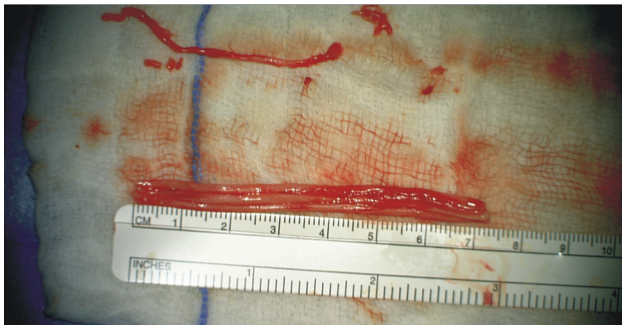

Fig. 2 (b) The gap is measured, the grafts are harvested and cut to the appropriate length

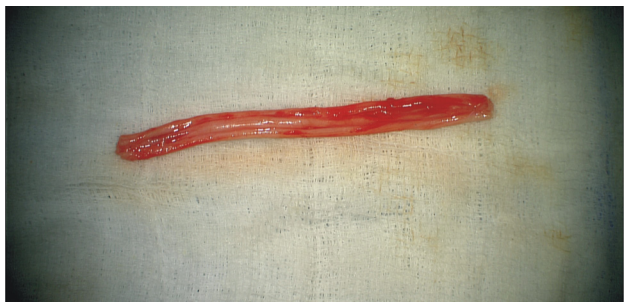

Fig. 2 (c) The nerve ends are cleaned from the soft tissues and grouped together using sutures

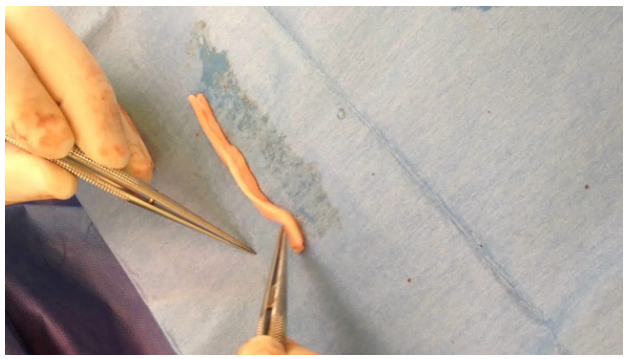

Fig. 2 (d) Fibrin glue can be used to group the individual grafts together prior to repair

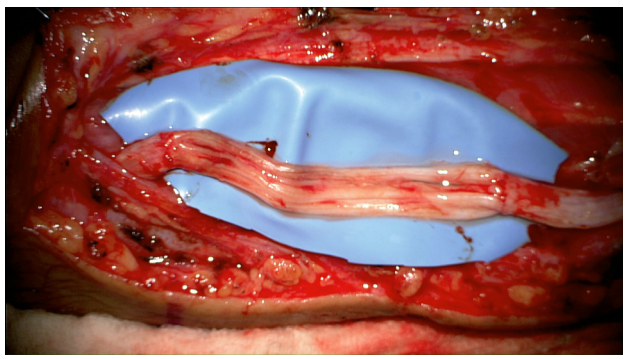

Fig. 2 (e) Note the lack of tension following completion of the repair

The sural nerve is the most commonly utilized donor nerve for grafting purposes, as it is easy to harvest, provides a good length (30-40 cm) and is associated with acceptable morbidity. Examples of donor nerves commonly used beside the sural nerve are the medial cutaneous nerves of the arm and the forearm (anterior division). Superficial sensory radial nerve gives a good 14 cm with diameter often larger than the sural nerve.

In general, the nerve graft should be about 10% longer than the actual nerve gap, as this allow mobility and avoids unnecessary tension on the repair.

Once repair is decided, the Penrose drains are removed, bleeding points from the bed are controlled,

irrigation with normal saline is performed, the graft is placed in the gap and both ends are sutured using 8-0 (rarely 9-0 or 10-0) non-absorbable monofilament micro-sutures. Magnification with loupes or the use of the operating microscope is necessary.

It is essential to remember that nerve suturing is a coaption rather than an anastomosis and tight repair is to be avoided. So the repair is basically an approximation of both ends. Tight suturing may cause overriding of fascicles or accordion effect, which may lead to pouting out of fascicle and misdirection of axons. The finer and the less the sutures material the less the fibrosis and scar reaction produced around the repair site. One or two sutures at each suture line, reinforced by fibrin glue, are usually sufficient. Following completion of the repair, both proximal and distal ends are inspected to ensure that loosing did not take place during the repair process. The fascia is not closed, and the wound is closed in layers with minimal manipulation to avoid disruption of the repair. The patient limb is immobilized for 3 weeks, and then a further 3 weeks of gradual range of movement are permitted.

Nerve Conduit (Tube) Repair

Despite being the gold standard in bridging the gap in peripheral nerve injuries, autologous nerve grafts come with several disadvantages such as donor site neurological deficit, need for additional incisions and chances of wound complications, neuroma formation and neuropathic pain, limited availability and so on. Only 40 to 50% of autologous nerve grafting shows useful degree of functional recovery[12]. These issues have paved the way to the study and use of non nerve grafts as a conduit for axonal regeneration. A tube works by encasing the distal and proximal nerve ends, guiding axons sprouting from the regenerating nerve end, protecting them from fibrous tissue and by providing a path for diffusion of neurotropic and neurotrophic factors from the injured nerve stump.

In a randomized controlled trial using nerve tubes, Weber and associates showed comparable clinical outcome to nerve autografts in repairing digital nerve gaps less than 3 cm[13]. Boeckstyns et al. compared collagen conduits and conventional neurorrhaphy in a prospective randomized controlled trial in 32 patients[14]. They concluded that collagen conduits gave useful recovery of sensory and motor functions similar to conventional neurorrhaphy at 2 year follow up when the gap was less than 6 mm. They also observed that the operating time was significantly shorter for collagen conduits. However, collagen conduits are also not immune to complications. Two papers have reported complications such as failure of resorption of the conduit, classic hourglassing of the fibrin matrix, fibrosis, scarring, neuroma formation and foreign body reaction on histological assessments[15,16]. In our opinion, commercially available tubes and decellularised allografts, which are devoid of Schwann cells and thus can fail to support regeneration[17], should be restricted to gap lengths of 25 mm with no larger than 30 mm tubes used. All other gap repairs should be repaired with nerve autografts.In practice, the senior author only uses nerve tubes for distal extremity (wrist, hand and foot level nerves) repairs where the gap length is 2 cm or less (Fig 3).

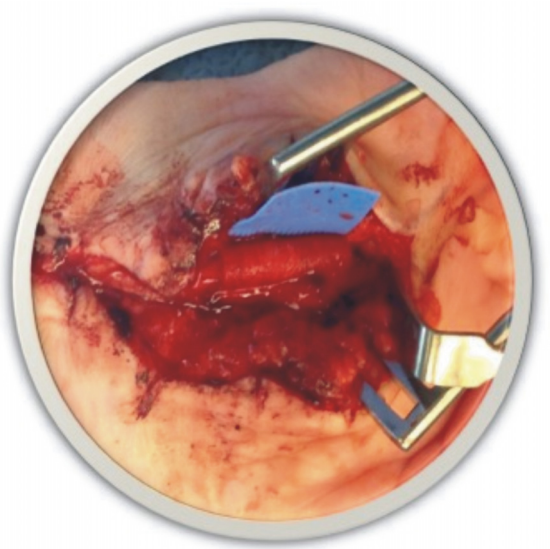

Fig. 3 A 1.5 cm gap in the deep branch of the ulnar nerve, following resection of traumatic neuroma, is shown being repaired with a 2 cm long collagen tube. The nerve at the proximal and distal end has already been placed within the lumen of the tube, awaiting repair with a single 9-0 microsuture at each end. The lumen of the tube following repair will be filled with saline using a small gauge (27) needle syringe.

Once the proximal and distal ends are prepared as for nerve autografts, an appropriate size nerve tube is chosen so that the inner luminal diameter is approximately 20% larger than the diameter of the nerve to repair. Both proximal and distal ends are inserted into both ends of the tube and a single “U” shaped suture is placed on both ends. Normal saline is used to fill the inner lumen to wash out tissue debris and maintain a fluid-filled lumen which will be quickly replaced by serum leaking form the ends of the nerve within the conduit. Fibrin glue may be used to reinforce the both ends of the tube following completion of the repair.

Limitations of Nerve Repair

Although surgical repair in most peripheral nerve injuries result in some degree of functional recovery, the results are suboptimal. This has been amply demonstrated in the classical literature and textbooks from several authorities[18-21]. Over the last two decades, there has been major improvement in the realm of surgical techniques used for nerve repair, including nerve transfers. However, many other factors such as the age of the patient, the location of the lesion (i.e. distance from the target muscle), type and timing of repair (primary versus secondary repair), type of nerve (single function or mixed nerve) and requirement for a graft are also known to have a major influence on the outcome[22]. The failure or inability to translate experimental results to the clinical realm has been an insurmountable issue. This has primarily been due to the difference in the slower rate of nerve regeneration and longer regeneration distances in humans, both of which are outside the control of the surgeon. This leads to a chronically axotomized distal nerve segment and chronically denervated end organ. The prolonged regeneration time subsequently leads to Schwann cell atrophy, inability to maintain basal lamina and disappearance of bands of Bungner and Schwann tubes[23,24]. In addition to this, endoneurial growth inhibitory molecules such as chondroitin sulfate proteoglycans are up-regulated in the regeneration phase which again contributes to the poor outcome[25]. The future of nerve repair would be promising if we can find a way to escalate the rate of nerve regeneration and to reverse the changes in the distal nerve segment.

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