

Novel Approaches of Nerve Repair and Regeneration in Maxillofacial Region

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ABSTRACT

Nerve injuries in maxillofacial region can occur secondary to trauma, neurological disease or tumor excision. These nerves have the tendency to regenerate, however, due to a number of confounding factors; this is often both incomplete and inadequate. So, there is need of novel approaches to regenerate nerve cells along the distal and proximal cut ends of the nerve for regaining normal functioning following nerve repair. With further developments, at the nano level, additive fabrication aligned with bioengineering technologies offers the potential for effective neural regeneration. By combining methods to create multimodal techniques, more significant improvements in nerve regeneration will be seen. In this review, we have discussed various current nerve repair strategies and the advanced nerve regeneration modalities in use.

Abbreviations: PGA: Polyglycolic Acid; NGF: Nerve Growth Factor; BDNF: Brain-Derived Neurotrophic Factor; GDNF: Glial Cell-Derived Neurotrophic Factor; CNTF: Ciliary Neurotrophic Factor; MGF: Mechano-Growth Factor; VEGF: Vascular Endothelial Growth Factor; FGF: Fibroblast Growth Factor : SMDF: Survival Motor Neuron-Derived Factor; MSCs: Mesenchymal Stems Cells; iPSC: Pluripotent Stem Cells

Introduction

Nerve lesions and defects can seriously interfere with the individual's ability to function adequately and the acquired disability is often dramatic. The quality of life for the patient is also impaired greatly, with the possibility of lifelong functional impairment, pain and paresthesia/dysesthesia [1]. In addition to complete defects of the nerve trunk, chronic nerve compression also represents a substantial problem [2]. Injuries to the nerves in the maxillofacial region can occur in multiple clinical scenarios such as dentoalveolar surgery, dental implants placement, orthognathic procedures, excision of tumors, local anesthetic injections and due to maxillofacial trauma or surgical interventions for facial trauma repair [3]. The amount of reinnervation and recovery is dependent on many factors such as the type of injury, anatomical site of the injury, interclump gap, alignment of nerve stumps and type of repair [1]. Despite the superior understanding of pathophysiological mechanisms and

advances in microsurgical repair techniques, nerve repair techniques continue to be a major clinical challenge. The standard repair strategy for repairing large gaps in transected nerves is a nerve autograft [4]. But this method has its own limitations because of donor site morbidity, required secondary surgery, and limited donor tissue availability [1]. These limitations of autografting have led to the search for alternative techniques like the use of tissue engineering to fabricate tissues that mimic the nerve autograft and thus helps in peripheral nerve repair [2].

Nerve Repair Techniques

Nerve grafting

For nerve injuries that do not involve a gap- tension-free primary neurorrhaphy is the method of repair. It is generally agreed that gaps in nerve continuity should not be repaired under tension but

rather should be bridged by nerve grafts. According to Millesi, the use of autologous nerve grafts is the method of choice for bridging gaps in nerve continuity [4]. The most common choice is the sural nerve, because of its desirable thickness, length and easy harvesting from lower limbs.³ In maxillofacial region use of hypoglossal nerve and great auricular nerve has also been reported for the lingual nerve and facial nerve repairs. However, this technique is associated with donor site morbidity [1].

End-to-side anastomosis

End-to-side (ETS) anastomosis of nerves, dates far back more than 100 years ago. In 1903, Balance et.al, used the principle of terminolateral neurorrhaphy by anastomosing the distal stump of an injured facial nerve to the accessory nerve. This principle was also used to treat an injury to the superior trunk of the brachial plexus by anastomosing the distal nerve to the intact seventh cervical root [5].

Nerve transfers

In cases when a proximal nerve segment is not available, an alternate donor nerve is needed to provide the distal segment of the injured nerve with axonal input from a proximal nerve segment. Such technique requires sacrifice of the donor nerve [5]. The required criteria for the autologous donor nerve must include- close coaptation to the target muscle, should preferably innervate a muscle, synergistic to the target muscle, should be expandable with large number of pure sensory axons and it should be situated near the original target skin area [3].

Free Vascularized Nerve Grafts

The concept of vascularized nerve grafts for clinical use was introduced by Taylor and Ham (1976) [6]. Regenerating axons have been reported to grow at a greater speed in vascularized nerve grafts than in free nerve grafts.⁷ Due to the time and technical expertise requirement, vascularized nerve grafts must be reserved for cases in which normal revascularization of the grafts cannot be expected to take place due of scarring [8].

Veins as conduits

Autologous blood vessels have also been tried as a tubular structure for bridging gaps in nerve continuity. Clinically experimental gaps of 4 to 15 mm in length have been bridged successfully. In an experimental rabbit model, good axonal growth has occurred through vein grafts up to 30 mm in length [9]. In patients, successful reconstruction of peripheral nerves with a gap length of up to 3mm or less has been reported [10]. With an interposed autologous nerve piece inside the vein, regeneration over distances up to 5.8 mm has been reported [11].

Vein-Muscle Conduits

Main disadvantage with the use of only vein conduit is their tendency to collapse from external tissue pressure. Battison, who used

combined vein-muscle conduits for bridging gaps, addressed this issue [12,13]. Fresh muscle tissues, introduced inside the vein conduit, prevents collapse and keeps the vein expanded, and also provide basal laminae to support axonal overgrowth [13]. Encouraging results from clinical use of the combined vein-muscle conduits have been reported.

Biodegradable Polymer Tubes

Positive data resulted from the experimental use of biodegradable polymer tubes, such as polyglycolic acid (PGA) [14]. This material has been used also in clinical practice. The concept is that the tube structure would allow successful regeneration and will be resorbed spontaneously with no need for surgical removal [15,16]. It was found that PGA conduits were useful and well comparable to the nerve grafts and end-to-end repair.² Many authors claimed that the nerve guides were superior to direct repair for gaps 4 mm or less and that a deficit of 8 mm or greater showed a difference in nerve grafts in favor of the conduits [17]. A PGA tube was also successful in the reconstruction of a 25-mm defect in the right inferior alveolar nerve [18].

Collagen Tubes

Among several bioresorbable alternatives to the nonresorbable silicone tubes are collagen tubes, which represent an interesting alternative with significant clinical potentials [19,20]. Collagen tubes have been shown to support regeneration over nerve defects in rats and mice [21-23] rabbits, [21] as well as primates [24]. Krarup and coworkers performed extensive studies on the use of collagen tubes in primates with special reference to factors that might influence regeneration.²⁴ Collagen-based nerve guides successfully bridged nerve gaps up to 5 mm [25].

Nerve Regeneration Techniques

Conduit lumen fillers

Addition of a growth guide into the lumen of nerve conduits improves the functional outcomes after nerve repair [26,27]. Biodegradable aligned polyamide fibers have been reported to be used in the lumen of nerve conduits which gave successful results in nerve repair in rats of about 10 mm to 15 mm [28]. Recently, nanofibers as lumen fillers have also been tried in the form of nano meshes made from blended PCL-laminin electro spun fibers of 100 nm to 200 nm diameters in nerve conduits for repair of 10 mm defects in rat tibial nerve [29,30].

Growth factors

Absence of sustained neurotrophic stimulation can be accounted for one of the reasons for limited capacity of reinnervation with nerve conduits in restoring larger defects. To address this deficiency, a number of neurotrophic factors have been employed in nerve repair including: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor

(GDNF), ciliary neurotrophic factor (CNTF), neurotrophin 3, 4, 5 (NT-3,-4,-5), mechano-growth factor 1 (MGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF-2), and survival motor neuron-derived factor (SMDF) [31,32]. Techniques for control of growth factor delivery have received attention, namely “core-shell” nanofibers and genetically modified cells. “Core-shell” nanofibers comprise a growth factor-laden core and a shell made of biodegradable polymers. As an alternative approach to viral-based gene therapies, plasmid-based gene delivery has also been used [11].

Stem cells

The lack of activated glial cells is postulated as one of the main reasons underlying the poor recovery after nerve injury. Conduits seeded with Schwann cells have been used successfully to repair 2 cm defects in rat sciatic nerve, with functional recovery equivalent to nerve autograft at 6 months post-surgery [5]. Autologous neural stem cells, mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSC) provide alternative sources of trophic cells to autologous Schwann cells for neural tissue engineering. Neural stem cells have been shown to improve nerve myelination and regeneration when grafted into chitosan-based nerve scaffolds. The main mechanisms that MSCs promote nerve regeneration are

- a. Secretion of neurotrophic factors and
- b. Trans-differentiation of the cells into glial-like cells that are directly incorporated into the growing nerve [31,33].

Electrical stimulation and conducting polymers

Electrical stimulation has the potential to promote neural and glial cell proliferation at the cellular level as well as axonal outgrowth in vitro and in vivo. According to Dellon, using rat femoral nerve model, it was found that 1 hour of 20-Hz continuous electrical stimulation of the parent axons proximal to the repair site effectively reduced the delay in outgrowth of motor fibers and improved motor reinnervation [32,33]. Current reports have discussed about the use of organic conducting polymers (OCs) as conducting structures in conduits. The commonly implemented conducting polymer for tissue engineering is polypyrrole. This polymer shows excellent biocompatibility and acts as a good structural and ‘active’ scaffold in promoting neurite growth under electrical stimulation in vitro as well as in vivo. Recently, chitosan-based nerve conduits have been evaluated for delivering electrical stimulation to enhance nerve repair in vivo [33,34].

Nanoparticles

Biodegradable scaffolds using collagen type-I and gelatine as main materials in combination with nano-silver particles and the laminin protein evenly distributed at the inter surface of the microtubules [21]. The nano-silver containing scaffold showed a higher rate of laminin adsorption, regenerated a nerve with a thicker

myelin sheath and improved the nerve conduction velocity and nerve potential amplitude. These results demonstrate the superior functionality of the nano-silver–collagen scaffold in the adsorption to laminin and subsequent regeneration of damaged peripheral nerves [26]. Even silk-gold nano-composite based nerve conduit is successfully tested in a neurotmesis grade sciatic nerve injury model in rats [29].

Bipolar radiofrequency

Bipolar radiofrequency treatment induced degeneration of sensory nerve fibers immediately after treatment, but by 90 days post-treatment, there was evidence of complete regeneration. Recently extracorporeal shock wave therapy (ESWT) and bipolar radiofrequency (bRF) micro-tenotomy have been used [21].

Low-Power Laser application

The use of vein graft with fat and the laser application leads to a better nerve regeneration, considering the fiber area and diameter, myelin sheath area and thickness parameters, compared to the treatment with vein graft only. The association between the vein graft with fat and the laser application enhanced the regeneration for all parameters (including also axon diameter and area). According to Buchaim et. al, this treatment significantly enhanced the fiber diameter ($6.94 \pm 0.43 \mu\text{m}$) and the myelin thickness ($4.04 \pm 0.37 \mu\text{m}$) compared to EG (3.43 ± 0.37 and $1.45 \pm 0.22 \mu\text{m}$, respectively [35]. The use of the vein graft fulfilled with fat tissue and the Low-Power Laser application enhance the nerve regenerative processes.

Future Directions and Conclusion

Developments in nanofabrication, polymers, gene and growth factor delivery and stem cell technologies enable new features to be incorporated and combined as a multifactorial approach for the design of nerve conduits. Sensory and motor regeneration are major hurdles that must be addressed.

Tissue engineering and nanotechnology are suggesting new research therapeutic approaches, potentially orientated to accelerate nerve regeneration and recovery of nerve functionality tissues. The developments in bio-synthetic nerve repair and additive fabrication technologies (e.g., 3D printing of materials, cells and scaffold substrates) have the potential to provide surgeons with the means by which to digitally capture the dimensions of a nerve injury for tailored “printing” of scaffolds for nerve repair.

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