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Review

Advances in peripheral nervous system regenerative therapeutic strategies: A biomaterials approach

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ABSTRACT

Peripheral nerve injury is a very common medical condition with varying clinical severity but always great impact on the patients' productivity and the quality of life. Even the current 1st-choice surgical therapeutic approach or the “gold standard” as frequently called in clinical practice, is not addressing the problem efficiently and cost-effectively, increasing the mortality through the need of a second surgical intervention, while it does not take into account the several different types of nerves involved in peripheral nerve injuries. Neural tissue engineering approaches could potentially offer a very promising and attractive tool for the efficient peripheral nerve injury management, not only by mechanically building the gap, but also by inducing neuroregenerative mechanisms in a well-regulated microenvironment which would mimic the natural environment of the specific nerve type involved in the injury to obtain an optimum clinical outcome. There is still room for a lot of optimizations in regard to the conduits which have been developed with the help of neural engineering since many parameters affect the clinical outcome and the underlying mechanisms are still not well understood. Especially the intraluminal cues controlling the microenvironment of the conduits are in an infantile stage but there is profound potential in the application of the scaffolds. The aim of our review is to provide a quick reference to the recent advances in the field, focusing on the parameters that can significantly affect the clinical potentials of each approach, with suggestions for future improvements that could take the current work from bench to bedside. Thus, further research could shed light to those questions and it might hold the key to discover new more efficient and cost-effective therapies.

Contents

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1. Introduction

Since the first Nerve Guidance Conduit (NGC) was used in 1882, when the first attempt was made to bridge the 30 mm nerve gap of a dog with a bone graft, many advances have been made [1,2]. Nowadays, the use of an artificial conduit to repair a peripheral nerve defect is a reality in clinical practice, although the 1st-choice surgical approach is considered the use of an autograft. The critical size to use a nerve conduit is still small, around 4 cm in length [3,4], but the promise of nerve engineering to substitute the use of autografts and allografts seems more realistic than ever. In this review all the new techniques and recent advances for making a peripheral nerve conduit will be analyzed. In addition, clinical problems and future directions for conduits to become the new clinical 1st-choice management plan (frequently referred to as the "gold standard") will be discussed extensively.

2. The clinical need

Peripheral nerve injury is very common especially in University hospitals and metropolitan areas where it is usually treated [5]. Their frequency is as reported 3% in all trauma patients and it rises up to 5% if plexus or root avulsion cases are included [6–8]. Most of the nerve injuries occurred in the upper extremities (81%) and 11% in the lower extremities [9]. For example, a very common peripheral nerve injury is the the one of the radial nerve, followed by the ulnar and the median, thereafter making the upper limb very often dysfunctional [10,11].

There is great variability in the severity of a Peripheral Nervous System (PNS) injury with symptoms ranging from severe, with significant loss of function or intractable neuropathic pain, to mild, with only certain sensory or motor deficits, but in any case, the injury greatly affects the quality of life of the patient. In addition, the variability of injuries in terms of their length makes it necessary for the bridging of the gap to expand from millimeters to several centimeters in length [12]. This is one of the greatest challenges that need to be met.

What are also underestimated, are the significance and the potential effect of the different types of peripheral nerves on the applied therapeutic strategy. There are three different types of peripheral nerve for reconstruction depending on their composition in nerve fibers; the pure motor, the pure sensory and the mixed peripheral nerves [13]. Although all the three types of nerves are useful in the human body it is evident that the pure motor and the mixed type of nerve are the ones which have a great clinical significance but currently mostly sensory nerves are involved in the ongoing therapeutic strategies due to easier harvesting and relatively lower donor-site morbidity [14]. Thus, there is a great need in addressing the nerve defect in accordance to the type of the nerve involved to get a good clinical outcome.

3. The animal models for peripheral nerve injury

Many different animal models have been used to test different approaches for the peripheral nerve injury. According to Angius et al. in an extensive review of literature the rat is the most commonly used small animal model and the rabbit the most commonly used large animal model. Nevertheless, there are no standardized animal models that are extensively used to measure and compare the effectiveness of each approach to nerve recovery [15]. This means that is very difficult to translate an approach because even the agencies for the approval of a clinical trial like Food and Drug Administration (FDA) do not have a standardized pipeline that can assess which approaches worth getting to clinical trials. Thus, the need for creating such a pipeline is crucial for bringing more methods from bench to bedside.

4. Current "gold standard" nerve guidance conduit

To date, the 1st-choice surgical approach, referred as to "gold standard", for bridging a peripheral nerve injury is the use of a graft taken from the body of the patient (autograft), regardless of the length of the gap. The autograft technique entails the use of functionally less important nerves such as sural or superficial cutaneous nerves as donors in order to be used in the site of the injury [16,17]. Many limitations exist with this technique making the need of a new way to bridge the peripheral nerves impelling. For example, the patient needs to undergo a second surgical procedure in order for the graft to be taken. In addition, the area where the graft was taken from is debilitated and functionally impaired, thereafter making the whole procedure difficult in application due to lack of autografts and surgical consequences. Furthermore, long-term, the patient is at risk of a neuroma formation in the transplanted area. Finally, from the economic point of view, the whole procedure is very expensive [5,18].

5. The allograph

An alternative option to use in nerve transplantations is cadaveric allografts [19,20]. Even though this technique comes with a great advantage, allowing the choice of the exact type of graft according to the patient's needs, there is also a great disadvantage; it requires systemic immunosuppression for approximately 18 months [21], thus increasing the risk of secondary infection and tumor formation [20,22]. Another approach that seems very promising is the use of detergents to make the nerve graft non-immunogenic, thereby overcoming the obstacle of systemic immunosuppression [23,24]. Recently AxoGen© claimed that their allograft named Avance® Nerve Graft has no disadvantages related to immunogenicity due to decellularization. Their on-going study, the Ranger® Study, had >600 nerve repairs enrolled in January 2015 and very promising preliminary results to show. The recovery rates were on average above 78% in a group of 109 subjects, with 151 nerve repairs performed using Avance® Nerve Graft [25]. The average gap length though, as previously reported by many other previous studies using nerve grafting, did not exceed the 4 cm and the decellularization techniques need to be optimized for more uniform and replicable results globally.

6. Veins and arteries as graphs

The last resort for the surgeons in order to fill the peripheral nerves gap after a trauma is the use of veins, and very rarely arteries, as conduits [26,27]. These grafts were showed to induce neuroregeneration and the technique is used in clinical practice. Unfortunately, the critical gap of 3 cm compared to the "gold standard" of the autograft was not surpassed [27–30].