Morini S, et al., J Stem Cell Res Dev Ther 2021, 7: 072
DOI: 10.24966/SRDT-2060/100072

HSOA Journal of
Stem Cells Research, Development & Therapy

Commentary

Clinical Considerations on Nerve Regenerative Techniques: a Commentary on the Article "Mesenchymal Stem Cell Treatment Perspectives in Peripheral Nerve Regeneration: Systematic Review"

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Traumatic lesions of peripheral nerves affect hundreds of thousands of patients every year. The consequences are often devastating mainly because nerves spontaneous recovery is frequently inadequate.

Cell therapy is one of the most innovative approaches in the field of nerve repair therapies.

In our previous article the features of the most promising types of MSCs for peripheral nerve regeneration after nerve injury have been discussed [1]. Techniques of stem cells delivery (such as micro-injection) in the lesion site, and the use of nerve conduits (when primary closure is not possible) have been revised. Although nerve lesions treatment with mesenchymal stem cells (MSCs) results in improvement in functionality of the affected limb, the comparison between the studies did not allow any significant analysis to identify a more effective MSC type or treatment modality among the others.

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Citation: Morini S, Lavorato A, Vincitorio F, Garbossa D, Battiston B, et al. (2021) Clinical Considerations on Nerve Regenerative Techniques: a Commentary on the Article "Mesenchymal Stem Cell Treatment Perspectives in Peripheral Nerve Regeneration: Systematic Review". J Stem Cell Res Dev Ther 7: 072.

Received: April 20, 2021; **Accepted:** May 18, 2021; **Published:** May 25, 2021

MSCs can be obtained from several sources: bone marrow (BMSC), subcutaneous white adipose tissue (ADSC), fetal tissues such as umbilical cord blood, Wharton's jelly (UCMSC), avascular amniotic mesoderm (AMSC), dental pulp tissue of adult / permanent teeth (DPSC) and skeletal muscles (SkSC) [1].

BMSCs are the first MSCs studied for nerve regeneration. Under particular conditions, they may exert their function through paracrine/autocrine activity [2]. BMSCs are very highly available, and highly used in pre-clinical studies [2]. On the other hand, the collection procedure is highly invasive, and this represents a limitation for their use.

ADSCs (adipose-derived stem cells), MSCs collected from adipose tissue, are a more accessible and clinically feasible source. These stem cells display a higher proliferative rate in culture compared with BMSCs [3]. ADSCs are extremely highly available, with a minimally invasive collection procedure, an extremely low immunogenicity and a very high survival rate after transplantation.

Dental pulp stem cells (DPSCs) require an invasive procedure of collection, have a very low immunogenicity, and express neural and Schwann cell phenotype after stimulation in vitro [2].

Fetal stem cells (Fetal SCs) represent a primitive source of MSCs [4]. Amniotic (AMSCs) mediate neovascular trophism and exert neurotropic effects. They can apparently differentiate into neural tissue under specific in vitro conditions, but due to the difficulty of finding embryonic tissues due to the ethical dilemma of using human embryos they are not generally used [4].

Umbilical cord (UCMSCs) stem cells are immunologically inert, and can synthesize trophic factors as glial cell line-derived neurotrophic factor (GDNF) [5] and vascular endothelial growth factor (VEGF) [5]. A few reports of tumorigenesis in transplantation experiments of UCMSCs have been published [4].

Skeletal muscle stem cells (SkSCs) are MSCs quite available, with an invasive procedure of collection. They represent an opportunity to reconstruct the muscle-nerve-blood-vessel unit due to their ability to differentiate into multiple lineages including myogenic, adipogenic and osteoblastic lineages [2,4].

Different techniques are used for stem cell delivery in the site of nerve lesions:

Local micro-injection of stem cells in the site of injury is a method under study, but the high pressure in the syringe could cause an ultrastructural trauma, inhomogeneous distribution of cells and could be less precise especially with the use of a large needle to avoid cell injury [4,6].

Intravenous injection, could prevent possible nerve damage and cell leakage, however these cells may not reach the site of injury due to capillary entrapment [6,7].

Nerve conduits are useful to bridge the gap when primary closure is not possible, and for their potential as a platform for stem cells delivery [8].

Natural nerve conduits are derived from biological tissues (muscle properly treated, veins, arteries). Artificial nerve conduits can be absorbable (biodegradable), and are advantageous because of their biocompatibility porosity and mechanical strength [9]. They offer the possibility of attaching Schwann cells and delivering them during biodegradation [10]. Nonabsorbable materials (silicon tube, elastomer hydrogel) have the disadvantage of engendering chronic foreign body reactions due to their inflexibility and scar tissue formation [9].

To deliver stem cells into nerve conduit lumen cells can be either suspended in medium [11] and injected into a hollow nerve conduit (the simplest and well-studied method providing least structural support for transplanted cells); suspended in a supportive matrix [5,12], which is then injected into the lumen of a hollow nerve conduit (tailoring the extracellular environment) ; or co-cultured directly in or on biomaterials used to fill the lumen of a complex nerve conduit [8]. This last technique has the greatest potential for tissue engineering [8] but is the most complex.

Summarizing the main characteristics of the different MSCs, ADSCs emerge as the most suitable for peripheral nerve recovery, due to their ability to support and stimulate axonal growth, their remarkable paracrine activity, their presumed differentiation potential, their very low immunogenicity and the high survival rate after transplantation [1,13].

Further clinical trials to confirm the safety and efficacy of ADSCs in PNIs are necessary. A clinical trial with the use of ADSCs in last-chance surgery in PNIs (neurolysis and nerve release) on a previously reconstructed nerve is ongoing. Patients enrolled will be observed and documented clinically and electrophysiologically for 2 years. They will receive once 10 microinjections of ADSC along the injured nerve directly after neurolysis. Safety, adverse events, and efficacy will be confirmed by clinical, electrophysiological (EMG and sensory threshold), and DASH (Disabilities of the Arm, Shoulder and Hand) surveys (ClinicalTrials.gov identifier: NCT04346680).

Furthermore, to better understand which combination of stem cell sources (potentially ADSCs) and conduit types represent the best option in the treatment of PNIs, further studies are needed to define and correlate clinical results and histomorphometric measurements in animal and in human models.

Nevertheless, some additional clinical nuances must be considered.

The included studies were carried out mainly on iatrogenic rat nerve injuries (neat or crushed) [11,14,15]. Only one of the studies considered involved nerve injuries in humans, specifically median or radial nerve injuries [16].

From a clinical point of view, functional recovery after a nerve lesion is conditioned by the distance between the nerve lesion and its target, but even most importantly by the traumatic mechanism characteristic: the best outcome (in terms of speed of recovery and regeneration) occurs when the injury is neat, without the stretching of the nerve [1,17].

Since the mechanism of a neat lesion of the nerve is easily reproducible, it is often observed in most of the nerve injury research models. Accordingly, the mechanisms of nerve degeneration and regeneration analyzed in these studies are more representative of this type of injury.

However, in clinical practice stretch-related nerve injuries are the most commonly seen type [18,19]. Probably inflammatory cellular mechanisms of tissue repair and surgical technical difficulties are related to poorer outcomes in these cases [11].

The correct timing for nerve reconstruction is still an open debate. If it is not clear whether there is nerve continuity, the clinical course of the motor and sensory deficit could help the surgeon in the decision making and timing for surgery. On the other hand, in the absence of nerve continuity, a nerve graft surgery performed within 6 months of the injury is associated with better functional outcomes allowing nervous fibers to reinnervate their muscle targets before they undergo irreversible atrophy.

Just as common in clinical practice, acute compressive neuropathies (e.g. "Saturday night palsy") and chronic entrapment neuropathies, causing venous congestion of the microcirculation of the nerve and reduction of axoplasmic transport, do not involve a rupture or tearing of the neural elements [18]. These physiopathological mechanisms of nerve injury and recovery could not be investigated in research models that do not reproduce this type of nerve lesion.

Nerve autograft treatment is the method of choice when primary closure is not possible and a gap between the two stumps needs to be filled [20].

This technique has some disadvantages, including donor site morbidity, limited length of graft, and the possibility of multiple surgeries [10]. In this regard, nerve guides represent a promising technique: beyond bridging the nerve gap, they permit the diffusion of neurotrophic and neurotropic derived factors to the nerve stump to mimic some autologous nerve graft properties [21].

Distance between the nerve injury site and its muscle target represents another important factor for clinical outcome. The growth rate of a nerve is about 1 mm per day [18], while it is slowed for non direct coaptations or multiple lesions cases.

Studying the regenerative potentials of MSCs and their properties in functional recovery after nerve injuries is definitely mandatory for cutting-edge nerve lesion centers. Actual research on animal models gives indispensable information on molecular and biological mechanisms of nerve injury and recovery, which should be integrated with the other degenerative and inflammatory processes involved in complex polytraumas. What is observed for neat nerve lesions is similar to what the surgeon performs during nerve reconstruction surgeries, but it is still far away from the complex physiopathological mechanisms observed more frequently in human traumatic nerve lesions.

Nevertheless, achieving faster nerve regeneration after surgical nerve repair is vital in order to reinnervate target muscles before they undergo irreversible atrophy. Future research should focus on saving valuable time for improving the outcome of patients with peripheral nerve injuries.

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