Experimental Considerations Concerning the Use of Stem Cells and Tissue Engineering for Facial Nerve Regeneration: A Systematic Review

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Purpose: Peripheral nerve trauma results in functional loss in the innervated organ, and recovery without surgical intervention is rare. Many surgical techniques can be used for repair in experimental models. The authors investigated the source and delivery method of stem cells in experimental outcomes, seeking to clarify whether stem cells must be differentiated in the injured facial nerve and improve the regenerative process.

Materials and Methods: The following key terms were used: nervous regeneration, nerve regeneration, facial nerve regeneration, stem cells, embryonic stem cells, fetal stem cells, adult stem cells, facial nerve, facial nerve trauma, and facial nerve traumatism. The search was restricted to experimental studies that applied stem cell therapy and tissue engineering for nerve repair.

Results: Eight studies meeting the inclusion criteria were reviewed. Different sources of stem and precursor cells were explored (bone marrow mesenchymal stem cells, adipose-derived stem cells, dental pulp cells, and neural stem cells) for their potential application in the scenario of facial nerve injuries. Different material conduits (vases, collagen, and polyglycolic acid) were used as bridges. Immunochemistry and electrophysiology are the principal methods for analyzing regenerative effects. Although recent studies have shown that stem cells can act as a promising bridge for nerve repair, considerable optimization of these therapies will be required for their potential to be realized in a clinical setting.

Conclusion: Based on these studies, the use of stem cells derived from different sources presents promising results related to facial nerve regeneration and produces effective functional results. The use of tubes also optimizes nerve repair, thus promoting greater myelination and axonal growth of peripheral nerves.

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Injuries of the peripheral nerves are common and debilitating, resulting in considerable long-term disability. The incidence of peripheral nerve injury in developed countries is estimated at 13 to 23 per 100,000 persons per year. Peripheral facial nerve injury is a common problem, with causes of facial nerve damage including

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malignant parotid tumor surgery, trauma, and petrous bone surgery. Facial nerve defects are common in clinical practice and may lead to movement disorders of facial muscles, bringing patients great mental strain. Facial nerve defect repair has been a focus and a difficult problem in the medical field. After transection, restoration of nerve function is poor and the resulting functional deficits significantly decrease the patient's quality of life.[1]

With the advent of surgical techniques and instruments, microsutures have considerably improved the management of peripheral nerve injuries. Autografting of an intact nerve remains the gold standard of bridging a nerve gap defect for the peripheral nerve lesion.[2] However, there are some limitations of the autologous nerve grafting technique, including the limited number of donor nerves available, unesthetic scarring, wound infection, wound pain, relatively long surgical time, a learning curve for the success of nerve grafts, and poor regeneration. The genesis of tissue and genetic engineering has led to an intense interest in the application of neural tissue engineering to promote facial nerve regeneration. These neural tissue engineering approaches primarily depend on 3 factors: artificial neural rooms, neurotrophic factors, and cell cultivation (mesenchymal stromal and neural stem cells).[3]

Mesenchymal stromal cells (MSCs), including adipose-derived stem cells (ADSCs) and bone marrow mesenchymal stem cells (BMSCs), are multipotent adult stem cells derived from adipose tissue and bone marrow. They are considered an alternative cell source in tissue regeneration because of their sufficient availability, ready accessibility, rapid proliferation, multipotent differentiation properties, and successful integration into host tissue with immunologic tolerance.[4,5] BMSCs and ADSCs are superior candidate cells for autologous cell transplantation and promoting peripheral nerve regeneration, because they can be harvested by less invasive procedures and cultured with higher proliferation rates.[5,6] Their ability to trans-differentiate into Schwann cells (SCs) and their trophic effects and myelin-forming ability make them an excellent candidate to overcome the limited application of SCs in nerve regeneration.[7,8]

Neural stem cells (NSCs), a kind of specific primitive nerve cell, exist in the nervous system and can differentiate into neurons, astrocytes, and glial cells. In 2005, Parker et al[9] summarized the properties of NSCs as follows: *1)* NSCs possess multipotent differentiation and can produce 3 kinds of mature neural cells (neurons, astrocytes, and oligodendrocytes) in many regions; *2)* NSCs can produce homologous new cells after nerve tissue injury; *3)* NSCs can be continuously transplanted; and *4)* NSCs can renew themselves. The discovery of NSCs broke the conventional idea that neurons cannot reproduce themselves. At the same time, NSCs, which were regarded as a kind of suitable donor cell, have been used in tissue-engineered studies because they possess properties of multipotent differentiation, strong plasticity, high immigration ability, and low immunogenicity.[10,11]

Given the studies conducted in recent years, this systematic review aimed to make a bibliographic search on the use of stem cells in the regeneration of facial nerves and discuss methods considering delivery methodologies and regeneration advantages.

Materials and Methods

A systematic review was conducted using the following electronic databases: Medline, LiLACS, Scielo, PubMed, Science Direct, and Cochrane Library, surveyed from 2002 to 2012 and written in English. The key terms used in the database searches were *nervous regeneration*, *nerve regeneration*, *facial nerve regeneration*, *stem cells*, *embryonic stem cells*, *fetal stem cells*, *adult stem cells*, *facial nerve*, *facial nerve trauma*, and *facial nerve traumatism*.

Experimental studies were included that obtained and described techniques for peripheral nerve repair using stem cell therapy and tissue engineering as tools to optimize the regeneration process. The articles were selected according to the quality of details based on the following criteria: structure of the title and abstract, introduction, methods (immunohistochemistry and immunofluorescence protocols, microscopy, and stereological and statistical analyses), results, and discussion.

The studies considered relevant to the review were thoroughly examined and a set of criteria was applied for their selection and inclusion in this systematic review (cell source and type, donor and host animal, facial nerve injury, number of cells injected, reconstruction method, behavioral and tissue analyses, stem cell phenotype, and regeneration advantage conferred over vehicle). The abstracts and full texts were read and classified to select only those that provided the information necessary to the review. They also were sorted according to the potential risk of any type of bias.

Results

One hundred nineteen articles were obtained, but only 8 were selected (Fig 1). All the articles selected were experimental studies. Based on the abstracts, 69 studies were excluded. From 50 studies screened, 42 studies failed in at least 1 criterion and were excluded. No articles were found in the LiLACS, SciELO, or Cochrane Library databases. All articles