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REVIEW ARTICLE

PERIPHERAL NERVE GAP MANAGEMENT: ROCK-PAPER-SCISSORS

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ABSTRACT

Peripheral nerves injury is one of the topical medical, social and economic problems. One of the crucial factors of surgical treatment of nerve trunks injuries ensuring their successful regeneration is the precise and tight connection of the proximal and distal stumps. To fulfill this goal a whole wealth of suturing and adhesive materials, laser and high-frequency electric welding techniques were suggested.

Currently microsurgical autoneurografting, which is considered the gold standard, is preferred in repairing nerve trunks defects. However, although effective, this surgical intervention has certain limitations, including the injury at the site of donor nerve harvesting with subsequent hypo– or anesthesia, scarring of the donor site, instances of formation of the painful neuroma of the central stump of the cutaneous nerve, lack of grafting material in the case of significant defect of the injured nerve or during reoperation, mismatch between the bundle structure of the damaged nerve trunk and the grafted segments of the cutaneous nerve. This situation stimulates the search for alternatives to autoneurografting.

KEY WORDS: peripheral nerve injury, nerve defect, autoneurografting, alloneurografting, stem cells

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INTRODUCTION

Peripheral nerves injury is one of the topical medical, social and economic problems, since oftentimes they lead to disability of people of both reproductive and productive age [1]. One of the crucial factors of surgical treatment of nerve trunks injuries ensuring their successful regeneration is the precise and tight connection of the proximal and distal stumps. To fulfill this goal a whole wealth of suturing and adhesive materials, laser and high-frequency electric welding techniques were suggested [2-4].

AUTONEUROGRAFTING

Peripheral nerve injuries treatment seems quite challenging in those cases when the defect is located between the central and the peripheral nerve stumps and neurografting should be done. Currently microsurgical autoneurografting, which is considered the gold standard [5] is given preference to in repairing nerve trunks defects [6], However, although effective, this surgical intervention has certain limitations, including for instance, the injury at the site of donor nerve harvesting with subsequent hypo– or anesthesia, scarring of the donor site, instances when the painful neuroma develops at the central stump of the cutaneous nerve, lack of grafting material in the case of significant defect of the injured nerve or during reoperation, mismatch between the bundle structure of the damaged nerve trunk and the grafted segments of the cutaneous nerve [7, 8]. This situation stimulates the search for alternatives to autoneurografting, one of which – alloneurografting has been around for quite a long time, and the second one - the use of stem cells (SCs) is quite recent.

ALLONEUROGRAFTING

Alloneurografting is considered as an alternative to autografting, since it has a number of advantages. For instance, there are no limitations in the amount of grafting material, it is possible to select a nerve-donor segment matching the damaged nerve trunk in caliber and bundle structure, and no additional traumas to the cutaneous nerves are caused. The main disadvantage of alloneurografting is the immunological conflict between the recipient and the donor nerve [9,10]. In the 80th of the past century a method of peripheral nerves grafting by cryopreserved allograft was created, studied in the experiment [11] and found its use in the clinical setting [12]. Cryopreservation was shown to decrease immunogenicity of the nerve tissues [13, 14]. Experimental study of neurografting with cryopreserved allografts continued [15,16] and the method was successfully used in clinical practice [17-18]. Theoretically cryopreservation made it possible to create a bank of allografts and by thorough matching of donors and recipients by the major histocompatibility complex to avoid rejection reaction. However this way seemed to be too costly and the development has gone along the path of using fresh allografts and immune suppression [19, 20].

As immune suppressants cyclosporin A[21], tacrolimus (FK506) [14], and rapamicyn[22] were used. It was shown that short-term immunosuppression had not created long-term tolerance [23], but was sufficient for the recipient's neurolemmocytes to migrate to the graft and replace the similar donor cells [24].

Short-term immunosuppression in the clinical setting [25-28] ensured positive outcomes of alloneurografting in patients with peripheral nerves and brachial plexus injuries. Immune suppressing therapy during allografting of the nerve trunks was further developed in the form of the so-called "co-stimulatory blockade". In work[29] allograft of the tibial nerve of mice was made, followed by a three-day administration of a monoclonal antibody to the anti-CD-40-ligand, thereby blocking the CD-40/CD-40L co-stimulatory pathway. 60 days after grafting stable immunological tolerance [decreased levels of gamma-interferon, IL -4 and IL-2] was observed, which correlated with functional restoration of the *m. extensor hallucis*.

Under the conditions of sciatic nerve allografting in mice [30] immunosuppression was achieved by blocking the co-stimulatory pathways LFA-1/ICAM, CD-40/CD-40L and CD28/B7 [administration of the anti-lymphocytic antigen-1 [anti-LFA], anti- CD40-ligand [anti-CD40L] and cytotoxic T-lymphocyte immunoglobulin antigen-4 [anti- CTLA4Ig], which resulted in successful regeneration of axons.

In the study [31], blockade of co-stimulatory pathways CD-40/CD-40L, CD28/B7 and ICOS/ICOSL also led to the improved outcomes of sciatic nerve allografting in mice.

Taking into account that besides the blockade of four co-stimulatory pathways studied in alloneurografting, we currently know six more [32], it should be recognized that this strategy is quite promising and in the near future may be applied in the clinical setting.

Achieving better outcomes of alloneurografting depends both on the refining of microsurgical methods, and on implementation of molecular biology advancements into clinical practice [33]. In the study addressing the problems and achievements of alloneurografting [34], it is rightly noted that current developments in the field of neurobiology open prospects for the development of nerve allografting, which in future may surpass autoneurografting by its efficacy.

USE OF STEM CELLS

The history of using cell technologies to solve the problem of nerve trunks regeneration started with the grafting of Shwann cells (SchCs) into a nerve defect. SchCs are cells which dedifferentiate after nerve injury, transforming in fact into the unipotent stem cells [34-37]. Autologous neurolemmocytes had been cultivated in vitro, and their grafting into the conduit improved both morphological and electrophysiological indicators of the reparative process [38]. In recent years, the possibility of more efficient use of neurolemmocytes grafting has been demonstrated through the use of genetically modified cells. The authors used Schwann cells with neurotrophin-3[39], FGF-2[40], GDNF overexpression [41].

Nevertheless, the use of autologous neurolemmocytes to treat acute nerve damage may be complicated by the fact that a few weeks of cultivation may be required to obtain a sufficient amount of cells. From this perspective the idea of grafting allogenic Schwann cells looks attractive. They can be harvested in sufficient quantities, preserved in tissue banks and subjected to immunological screening for compatibility with the recipient, as is the case with organ transplantation. Such an attempt was made in the experiment, however the process of cell rejection "was way too fast" and regeneration of the nerve fibers did not substantially change compared with control [42]. Thus Schwann cells grafting, although developed in the experiment, have not found broad clinical application. And the next step was the search for stem cells [SCs] from different sources to be used as grafts of damaged peripheral nerves.

Walsh [43] found that stem cells grafting may be quite promising, useful and can enhance treatments of nerve injuries. In 2015 the World Journal of Stem Cells published a comprehensive review of the use of SC to stimulate peripheral nerves regeneration [44]. Detailed information about various sources of SCs, such as embryonal SCs, fetal SCs, neural SCs, bone marrow derived stem cells (BDMSCs), adipose tissue derived stem cells (ATDSCs), dermal SCs, hair follicle SCs (HFSCs), dental pulp SCs (DPSCs) and induced pluripotent SCs (iPSCs) was provided. The author concluded that ATDSCs represent the most promising source for grafting into the damaged nerve defect. Although alternative sources like BDMSCs, fetal SCs, HFSCs and DPSCs have large potential, their use is limited at present.

Moreover, the impact of olfactory ensheathing SCs (OESCs) and SCs from peripheral blood was also studied. Olfactory epithelium cells may be considered as a promising source for grafting into the damaged structures of CNS and PNS [45]. Grafting of Olfactory SCs into the damaged peripheral nerve revealed improved regeneration, which was confirmed by methods of morphometry [46] and electrical physiology [47]. Moreover, immunohistochemistry has proved that OESC exhibit features of the Schwann cells and myelinize the regenerating axons. After transplantation of Olfactory SCs, Schwann cells and their mixture it was found that in the latter case axon regeneration was most effective [46]. The authors believe that this is due to the stimulating impact of Olfactory SCs on Schwann cells.

Study of the spinal cord neurons reaction to nerve cutting revealed that use of OESC and even fragments of olfactory epithelium had greatly prevented neuronal death [48].

Mononuclears of human peripheral blood contain almost 0,04% CD133+ cells. Administration of these cells into the silicon conduit placed between the central and the peripheral stumps of the rat's sciatic nerve has significantly improved outcomes of its regeneration, which was confirmed by methods of electrophysiology and morphometry. It was also found that the grafted cells had differentiated into the Schwann cells and expressed S100 protein [49].

Another promising direction in the SC use for repairing nerve trunks defects is their use in conduits or scaffolds in accordance with the basic concepts of neuroengineering: 1) making in the laboratory setting active complexes for

Table 1. Strengths and limitations of neurografting methods

Grafting material	Injury at the site of harvesting	Scarcity of grafting material	Mismatch of the bundle structure	Mismatch of the caliber	Immunological conflict and the need for immunosuppression	Lengthy cultivation	Potential oncotransformation
Autografting	+	+	+	+	-	-	-
Allografting	-	-	-	-	+	-	-
Embryonal SCs	-	-	+	-	-	+	+
Fetal SCs	-	-	+	-	-	+	-
Neural SCs	+	-	+	-	-	+	-
BDMSCs	+	-	-		-	+	-
ADSCs	+	-	+	-	-	+	-
HFSCs	+	-	+	-	-	+	-
DPSCs	-	-	+	-	-	+	-
iPSCs	-	-	+	-	-	+	+

creating microenvironment corresponding to that in the nerve trunk; 2) seeding the conduits with these complexes, which are extremely important for the regeneration of nerve fibers and which are absent in the nonneural grafts [50]. Conduits have the form of small tubes of different diameters filled with biologically active substances, cells, micro- and nanofibers in various combinations.

Historically these tubes made of different materials for repairing nerve defects have been tested for over 100 years since the late 19th century. For this purpose very different biological and non-biological materials have been tried.

Unfortunately, the analysis of experimental and clinical material led to the conclusion that this method should not be overestimated. The success of this type of operations was observed only in cases of repairing small defects in the thin nerves. However, the emergence of new materials and techniques has revived interest in the use of conduits, and the last 4-5 years were marked by a real boom in the development of this trend [51].

The first conduits created according to the neuro engineering concept were segments of veins or biodegradable synthetic tubes enriched with growth factors and SchCs [52-55]. In Udina [56] study it was shown that regenerating axons have successfully crossed the 6-cm defect of the peroneal nerve in rabbits. The ideal conduit should be biocompatible, biodegradable, soft and flexible, its cover should be semi-permeable, prevent fibrosis and ingrowth of connective tissue into the lumen, ensure directed growth of axons, meet the technical requirements for further manufacturing, sterilization, long term storage and surgical use [57]. In [58] silk conduits with gold nanoparticles seeded with SchCs culture were used for this purpose. Successful regeneration of the rat sciatic nerve was observed after simulation of 10mm defect.

Conduits are increasingly used in clinical practice [59]. Use of neuroengineering approaches is promising [60] and in future is sure to give positive functional results along with the autoneurografts [61].

Over the last 3-4 years study of the SCs impact on peripheral nerve regeneration has continued. Thus the impact of BDMSCs [62, 63], HFSCs [64], DPSCs [65,66], cordal [67] and peripheral [68] blood has been studied. So, cell technologies are promising and can ensure improved results of nerve injury treatment. However, the number of works where cell technologies are used for the damaged nerve in clinical setting is still relatively small. Apparently, this is due to the lack of long-term results of SC transplantation and the caution regarding their possible oncotransformation or autoimmune process. Therefore, more profound fundamental studies in this area are needed.

So, each of the discussed methods has its strengths and limitations (Table 1). The current situation resembles the well- known game, which gave the title of this review. And although autoneurografting is currently the "gold standard", each of the other two methods has its own advantages and in the near future may receive the "platinum" status.

CONCLUSION

In concluding this review, it should be stated that the use of alloneurografts and conduits seeded with SCs in experiments on animals allowed to obtain positive results comparable to those of autoneurografting. In clinical practice autoneurografting remains the gold standard, however not free from limitations as discussed above. Alternative methods (alloneurografting, conduits) are successfully used for small defects of the thin nerves. Further development of immunosupression methods, reduction of immunogenicity of alloneurografts, and bioengineering will allow to create a method for bridging nerve trunks defects free from the limitations of autoneurografting and equal to it in efficacy.

ABBREVIATIONS

ATDSCs - adipose tissue derived stem cells
BDMSCs – bone marrow-derived mesenchymal stem cells

DPSCs -- dental pulp stem cells
HFSCs - hair follicle stem cells
iPSCs - induced pluripotent stem cells
OESCs - olfactory ensheathing stem cells
SchCs- Schwann cells
SCs – stem cells

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