Peripheral Nerve Surgery: Allo-Grafts and Conduits (Alternatives to Autografts?) in Peripheral Nerve Regeneration.

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Abstract

This article provides a review of some recently published studies, which share the search for a valid alternative option to the use of autologous nerve grafts in peripheral nerve repair. Five are experimental animal studies and the last reports on a clinical experience in humans. The first two papers studied the effectiveness of allografts compared with the classic use of autografts in animals transiently treated with FK 506 (Tacrolimus), an immunosuppressant with neuroregenerative and neuroprotective effects. The following three papers studied artificial conduits filled with cells. In the first of these papers, a nerve conduit of trimethylenecarbonate-co-epsilon-caprolactone was filled with autologous Schwann cells. In the second paper, the authors used artificial conduits filled with bone marrow stromal cells-derived Schwann cells. In the third paper, the artificial conduits were filled with blood-derived CD133+ cells. The last paper is a retrospective analysis of surgical outcomes in 5 patients with brachial plexus birth injury treated with an artificial conduit made of a biological material, a collagen matrix tube (Neurogen). At the end of this review, the role of autologous nerve autografts as the gold standard for peripheral nerve repair still remains. Allografts must resolve definitively the problem of rejection and immunosuppressant therapy. Conduits made of no biological materials filled with the cells cited in the reviewed papers are not competitive with nerve autografts and even with allografts. Collagen matrix conduits in humans seem competitive with nerve autografts for short nerve gaps (less than 2 cm).

Introduction

Peripheral nerve lesions are an important cause of disability, as they affect a highly productive age group and are treatable (7). The main surgical challenge in

complete peripheral nerve lesions is the reconstruction of the gap between the two nerve stumps: ideally the defect should be filled with material that induces and facilitates nerve regeneration, is easily and safely available and has no rejection issues.

Repair of peripheral nerve lesions has been traditionally achieved by using nerve autografts. The potential disadvantages of their use are: 1) donor-site morbidity, consisting of numbness in the target area of the harvested nerve; risk of development of painful neuroma, infection, etc 2) the limited availability of donor nerves; 3) the time-expense. Several alternative repair techniques have therefore been proposed. We then reviewed six papers, dealing with the issue of peripheral nerve regeneration after repair with alternative options to the use of nerve autografts (2-6, 8). Such alternative options might be divided in two main groups, based on the main material used to fill the nerve gap: 1) Nerve allografts, 2) Artificial conduits made either without or with biological materials and filled or not with cells of different origin.

The main deterrent in the use of nerve allografts is graft rejection. The use of immunosuppressant therapy combined with nerve allografts might replace the classic use of autografts, though the need of long-term medical therapy is a limit of allografts: the group lead by Gorria at the University of Navarra used a primate model to evaluate the transient use of Tacrolimus, an immunosuppressant with neuroregenerative and neuroprotective effects (3, 4).

A number of synthetic, absorbable and not absorbable, materials have been proposed to enhance and support nerve regeneration across nerve gaps (8). The ideal material should be: a) porous, to permit the diffusion of nutrients while preventing the invasion of scar-forming cells; b) biocompatible, without eliciting toxic reactions, and c) absorbed after termination of a successful regeneration across the gap. Although some materials demonstrated such properties and satisfactory results over short distances, the regenerating axons cannot bridge large gaps, probably because of the lack of cellular elements. For this reason, different researchers are experimenting different conduits filled with various cells. Three of the reviewed papers deal with this issue (5, 6, 8).

The importance of Schwann cells in peripheral axon regeneration is well known. Then, one paper focused on artificial conduits filled with Schwann cells7. However, a number of problems can arise and limit the use of Schwann cells, such as the isolation of a sufficient number of cells and ethical problems. Therefore, a useful alternative can be the use of neural lineage cells or progenitor/stem cells able to differentiate in Schwann cells. This is the reason why other researchers have focused on possible alternatives to Schwann cells. We then reviewed two studies that share this approach (5, 6).

The last paper reviewed the clinical outcomes of peripheral nerve repair with artificial conduits made by collagen in humans (2).

(1) PERIPHERAL NERVE REGENERATION THROUGH ALLOGRAFTS COMPARED WITH AUTOGRATFS IN FK506-TREATED MONKEYS (3)

Aubá C, Hontanilla B, Arcocha J, Gorría O

J Neurosurg (2006) 105(4):602-9

Information

The main problem in the use of nerve allografts for repairing nerves is graft rejection. Then, procedures able to reduce the antigenicity of nerve allografts and/or use of immunosuppressants are necessary. FK506 (Tacrolimus) is a new immunosuppressant with greater potential and fewer side effects than others; it has also neuroregenerative and neuroprotective effects (10).

In the present study eight male nonhuman primates were used. In a first group of 4 animals, seven injured ulnar nerves were repaired using 4 cm-long superficial fibular nerve autografts. In a second group of four animals, seven injured ulnar nerves were repaired using 4 cm-long superficial fibular nerve allografts previously cold-preserved for 3 weeks. The animals with nerve allografts were temporarily treated for two months with FK506. Eight months after nerve repair the following parameters were collected in both groups of animals: functional recovery, number of ulnar motor neurons in the spinal cord, number of axons in the distal nerve stump and nerve conduction velocity. Animals in both groups exhibited functional recovery of hypothenar muscles.

No statistically significant differences were found in the number of ulnar motor neurons in the spinal cord and the number of axons in the distal nerve stump in both groups of animals. The autograft group demonstrated a greater nerve conduction velocity than the allograft group, with statistically significant differences. Histologically, few inflammatory cells were observed in the autograft cases, whereas more connective tissue, fibrin, inflammatory cells around the vessels with some giant cells were detected in the allograft cases. The presence of more inflammatory cells, connective tissue and fibrin could indicate a partial rejection of the allograft after withdrawal of FK506 two months after nerve repair. Such partial rejection might cause loss of Schwann cells, demyelination of regenerated axons and a lower nerve conduction velocity in the allograft group of animals.

Analysis

The most important data of the study stems from the finding that clinical results obtained with cold-preserved allografts + temporarily FK506-therapy were similar to those obtained with the classic autograft; eight months after ulnar nerve repair all the monkeys exhibited an apparently normal function.

In both groups of animals, the anatomical results regarding the number of ulnar motor neurons in the spinal cord and the number of axons in the distal nerve stump were also similar. Then, clinical results were confirmed and correlated with the anatomical evaluation.

However, some criticism might be expressed about the accuracy of this study: in the "Materials and methods" related to the processing of the neural tissue it is written that "The middle and lower thoracic (?) spinal cord was cut…", which is probably a typographic mistake. More importantly, the low quality of the

histological examination of the nerves seen in Figures 3 D, 5 and 6 allows only a rather approximate morphometric study.

One of the problems in using nerve allografts is the decision about the duration of the immunosuppressant therapy: either for a limited period of time, the one strictly necessary to allow regenerating axons to cross the allograft, or unlimited (9)? In this study, FK506 was administered only for two months after surgery and six months later the monkeys exhibited a normal function recovery. At that time, the animals were sacrificed and the allografts showed signs of partial rejection: was this process active or extinguished? The question remains unanswered.

(2) NERVE REGENERATION THROUGH NERVE AUTOGRAFTS AND COLD PRESERVED ALLOGRAFTS USING TACROLIMUS (FK506) IN A FACIAL PARALYSIS MODEL: A TOPOGRAPHICAL AND NEUROPHYSIOLOGICAL STUDY IN MONKEYS (4)

Hontanilla B, Aubá C, Arcocha J, Gorría O
Neurosurgery (2006) 58(4):768-79

Information

The aim of this study was to examine the efficacy, in terms of nerve regeneration, of using cold preserved nerve allografts to repair a transected branch of the facial nerve in primates temporarily treated with FK506 compared with the classic use of nerve autografts. In the present study, eight male nonhuman primates were used. In a first group of 4 animals, seven injured middle zygomatic branches of the facial nerve were repaired using 3 to 4 cm-long superficial fibular nerve autografts. In a second group of four animals, seven injured middle zygomatic branches of the facial nerve were repaired using 3 to 4 cm-long superficial fibular nerve allografts previously cold-preserved for 3 weeks. The animals with nerve allografts were temporarily treated for two months with FK506. Eight months after nerve repair the following parameters were collected in both groups of animals: functional recovery, number of motoneurons in the brainstem facial nucleus, number of axons in the distal nerve stump, nerve conduction velocity (NCV) of the nerve grafts and the maximum amplitude of compound motor action potential (CMAP) of the zygomatic muscles. NCV refers to the nerve fibers myelinization and CMAP to the number of axons present in the nerves.

After 8 months, all the monkeys of both groups recovered a normal facial movement though the mean values of the CMAP and the NCV were significantly higher in the autograft group than in the allograft group. Histologically, few inflammatory cells were observed in the autograft cases, whereas more connective tissue, fibrin and inflammatory cells around the vessels with some giant cells were detected in the allograft cases.

All the nerves in both groups were structurally intact with Schwann cells presenting signs of atrophy in both groups, with vacuolization visible in thirty percent of Schwann cells in the allograft group. The presence of more

inflammatory cells, connective tissue and fibrin in the allograft group could be a further demonstration of a partial rejection after withdrawal of FK506.

Neuronal density in the facial nucleus in the autograft group was significantly lower in the allograft group, with 70% fewer labeled motoneurons as compared to the autograft group. However, the number of large motoneurons in both groups was not significantly different as well as the number of axons in the distal nerve stump, thus indicating that axonal collateralization occurred in the nerve allografts.

Analysis

To study the efficacy, in terms of functional recovery, of a modality of nerve repair it is advisable to use a transection of the main nerve trunk and not of one of its branches. In such a manner, the functional results obtained will be directly ascribed to the repair of that nerve and not to other hypothetical mechanisms. In this study, one of the branches of the facial nerve, the zygomatic one, was transected and then repaired by using either autografts or allografts+FK506 and the functional results in both groups were the same eight months later.

Though the number of motoneurons was 70% less in the allograft group compared with the autograft one, such anatomic result permitted the recovery of a normal facial function. For the authors, such result could be due to the fact that the number of large motoneurons in the allograft group was not statistically different in comparison with the autograft group.

Also, the number of axons, in the proximal and distal nerve stumps, was not statistically different in both groups. Very interestingly, about 57% of the axons were lost between the proximal and the distal nerve stump across either the autograft or the allograft. In fact, whereas in the proximal nerve stump the number of axons was 458 in the autograft group and 418 in the allograft group, in the distal nerve stump the number of axons was 198 in the autograft group and 177 in the allograft one. It seems surprising that, although the ratio between the number of axons in the distal nerve stump and the number of neurons in the facial nucleus was 1.04 in the control cases, 0.59 in the autograft group and 1.73 in the allograft group, such difference did not influence the functional recovery in both the experimental groups. However, this study demonstrated that an inflammatory reaction around the allograft was present at the end of the study six months after withdrawal of FK506. It appears possible that, after withdrawal of the immunosuppressant, the rejection occurs slowly allowing for repopulation of the allografts with autogenous Schwann cells, which progressively substitute the donor Schwann cells within the allograft. In any case, the results of this study were obtained in a limited period of time and then we do not know if a rejection of the allograft would occur during the duration of a normal life. Nerve allografts have not only the Schwann cells but contain also other cells in the connective sheaths and vessels. Also here the quality of the histology of nerves seen in Figure 5 is not the best for a precise quantitative axonal study.

(3) NERVE REGENERATION ACROSS A 2-CM GAP IN THE RAT MEDIAN NERVE USING A RESORBABLE NERVE CONDUIT FILLED WITH SCHWANN CELLS (8)

Sinis N, Schaller HE, Schulte-Eversum C, Schlosshauer B, Doser M, Dietz K, Rösner H, Müller HW, Haerle M
J Neurosurg (2005) 103(6):1067-76

Information

Four different groups were studied for this paper. Rats that did not undergo any kind of surgery served as the control group (Group 1). In the experimental rats, the gap of 2-cm created in the median nerve was repaired by using a nerve autograft (Group 2), a nerve conduit of trimethylenecarbonate-co-epsilon-caprolactone (TMC/CL) left empty (Group 3) and a nerve conduit of TMC/CL filled with autologous Schwann cells (Group 4). Periodically after surgery, the functional recovery was evaluated using the grasping test. Nine months after surgery, the following studies were performed: a) nerve conduction velocity across either the nerve autografts or the implants; b) weight of the flexor digitorum superficialis muscle to assess the degree of atrophy; c) number, density and size of axons and myelin thickness in a transverse section obtained at the distal end either of the autografts or of the implants.

Complete functional recovery was observed in animals repaired either with autologous grafts (Group 2) or with nerve conduits containing Schwann cells (Group 4). However, functional recovery was faster in Group 2 (24-26 weeks after surgery) than in Group 4 (32 weeks after surgery). No signs of functional regeneration were found in animals treated with the empty conduit (Group 3).
Nerve conduction velocity across the autografts or the implants in Groups 2 and 4 was similar to that of control rats (Group 1); no potential was recorded in Group 3.

The weight of the flexor digitorum superficialis muscle was similar in Groups 2 and 4; a marked decrease in muscle weight was seen in Group 3 indicating advanced atrophy.

Six months after surgery, the nerve conduits were macroscopically resorbed in both conduits-groups. A tissue cable bridged the gap of the median nerve and appeared atrophic in animals that had received an empty conduit.

Nine months after surgery, whereas axonal regeneration was found at the distal end of the nerve autografts or implants in Groups 2 and 4, only extensive scarring was seen in Group 3 animals. The number and size of axons and the myelin thickness were similar in Groups 2 and 4, the autograft Group 2 showing a trend nearer to the normal rats.

Analysis

We agree with the authors when they underline that the results of this study must be critically considered, because it is well known that axonal regeneration power in rats is stronger than in humans. Therefore, before application of conduits filled with Schwann cells for repairing nerves in humans further studies will be necessary.

Of the entire sectional area of the artificial conduit only a minimal part was occupied by regenerated axons as shown in Figure 8. Considering the results cited in the Table 3 and the Figure 10 of this paper, we can note that in comparison with the control-Group 1, the axon size in the Group 4 (conduit filled with Schwann cells) and in the autograft-Group 2 was -45% and -16% smaller, respectively. Furthermore, in comparison with the control-Group 1, the myelin sheath maturation also was better in the autograft-Group 2 (-23% thinner) than in the conduit filled with Schwann cell-Group 4 (-33% thinner). Then, the quality of axonal regeneration was better in the rats in which the median nerve was repaired with nerve autografts.

In conclusion, this paper confirms the well known importance of Schwann cells in peripheral nerve regeneration and demonstrates better anatomical results when the median nerve was repaired with nerve autografts instead of conduits filled with Schwann cells.

(4) PERIPHERAL NERVE REGENERATION BY TRANSPLANTATION OF BONE MARROW STROMAL CELL-DERIVED SCHWANN CELLS IN ADULT RATS (6)

Mimura T, Dezawa M, Kanno H, Sawada H, Yamamoto I
J Neurosurg (2004) 101(5):806-12

Information

Bone marrow stromal cells (BMSCs) can be induced to differentiate in Schwann cells by sequentially treating the cells with β-mercaptoethanol and retinoic acid, followed by forskolin and neurotrophic factors including heregulin-β1. In this study, a 12 mm-long gap was created after section of the sciatic nerve in adult rats. Then, the sciatic nerve was repaired using artificial conduits (12 mm in length) which were filled with Matrigel (containing laminin, collagen IV, transformin growth factor-B, and fibroblast growth factor) + BMSC-derived Schwann cells (BMSC-DSCs) in the experimental rats and only with Matrigel in the control rats. The artificial conduits were sutured (using 10-0 nylon strings) to both stumps of the transected sciatic nerve.

Five months after nerve repair, walking track analysis allowed the quantification of the sciatic nerve functional index (normal range = - 1.9 +/- 6.3). Six months after nerve repair electrophysiological evaluation (motor nerve conduction velocity) and immunohistochemical analysis at the level of the artificial conduit were performed.

Results of these studies showed the sciatic nerve functional index and motor nerve conduction velocity significantly better improved in the experimental group compared with the control group. Immunohistochemical study demonstrated that transplanted BMSCs labelled with green fluorescent protein were positive for markers of mature Schwann cells (P0 and myelin-associated glycoprotein) and had reconstructed nodes of Ranvier and remyelinated regenerated axons. The number of regenerated axons in the axial section of the central portion of the graft was significantly greater in the experimental group. Although BMSCs can differentiate into several types of cells, tumor formation did not occur six months after the procedure.

Analysis

The BMSCs should be a very good source for supplying donor cells and authors sustain that they could be a solution to current limitations in autotransplantation because they have great proliferative potential in humans as well as in rats.
Moreover, bone marrow harvesting is relatively less invasive, the method is free from foreign pathogen interference, there is no need for immunosuppressive therapy, and there are no ethical problems.

The number of regenerated axons in the axial section of the central portion of the graft was significantly greater in the experimental group. However, this study was made using a relatively short nerve gap (12 mm) in the rat in which the peripheral axon regeneration power is more vigorous than in humans. Furthermore, the six month duration of the study is not long enough to address the problem of tumor formation from the multipotential BMSCs. The eventual application of BMSCs in peripheral nerve repair in humans needs further experimental studies comparing their efficacy with nerve autografts in longer nerve gaps and with longer follow-up.

(5) REGENERATION OF PERIPHERAL NERVE AFTER TRANSPLANTATION OF CD133+ CELLS DERIVED FROM HUMAN PERIPHERAL BLOOD (5)

Kijima Y, Ishikawa M, Sunagawa T, Nakanishi K, Kamei N, Yamada K, Tanaka N, Kawamata S, Asahara T, Ochi M
J Neurosurg (2009) 110(4):758-67

Information

Peripheral blood–derived CD133+ cells are very accessible human cells for clinical applications; they are therefore a good candidate for transplantation to address neural defects. The CD133+ epitope is a marker of human hematopoietic/endothelial progenitors, a subpopulation of cells which displayed a great potential for the repopulation of bone marrow and the differentiation into mature endothelial cells in animal models. In peripheral nerve regeneration, vasculogenesis should provide an improved environment for axonal regeneration. In this study, CD133+ cells of human origin were transplanted to repair a sciatic nerve injury in athymic rats. A silicone tube, bridging a 15-mm long defect in the sciatic nerve, was filled with atelocollagen gel containing CD133+ cells or mononuclear cells (MNC), or being combined only with phosphate-buffered saline (PBS, control) (12 animals in each group). At 8 weeks postsurgery macroscopic observations of the grafted sites, molecular, histological, and electrophysiological evaluations were performed. Macroscopic findings demonstrated extremely poor continuities with scarlike tissues being recognized in only 2 cases in the PBS group. In 5 cases in the MNC group, nervelike tissues bridging the defects were observed; massive nervelike tissues bridging the defects were seen in all of the animals grafted with CD133+ cells.

Moreover, the number of myelinated fibers, axon diameter, myelin thickness, and percentage of neural tissue was significantly higher in the CD133+ cell-grafted Group compared with the other two Groups. CMAPs were observed in all

cases in the CD133+ cell–grafted group; clear CMAPs were not detected in all cases in the PBS and MNC groups thus demonstrating that functional axonal regeneration had been obtained only in CD-133 cell-grafted animals. Furthermore, whereas it was demonstrated that the transplanted CD133+ cells differentiated into Schwann cells, endothelial cells of human origin could not be observed in the new vessels.

These results suggest that CD133+ cell transplantation contributes to form an ideal local environment for acceleration of axonal regeneration by differentiating into Schwann cells and not by favouring vasculogenesis. Morphological and histological examination demonstrated enhanced reconstruction of neural tissue, abundant Schwann cells, and myelinated axons only after CD133+ cell transplantation, but this did not occur in the MNC and PBS group. The observation that transplanted CD133+ cells differentiated into Schwann cells in vivo is important. It is known that the Schwann cells have a role not only for myelination of axons in the peripheral nerve, but that it also secretes neurotrophic factors leading to axon regeneration.
Analysis:

Transplantation of CD133+ cells in an injured peripheral nerve environment induces axonal regeneration; the CD133+ cells differentiate into Schwann cells and not in endothelial cells. Though, practically, CD133+ cells can be easily isolated from peripheral blood and could be applied as an autologous therapeutic agent with no limitation due to ethical or technical problems, they can be used in peripheral nerve repair only in an artificial conduit. As in other experimental studies with artificial conduits only a minimal part of their cross-section was occupied by nerve regeneration represented by rather poor axonal regeneration in terms of low number and small diameter of the regenerated axons if compared with what is seen using nerve autografts and also nerve allografts. The electrophysiological data obtained in this study confirm our view; no real functional results in terms of motor and sensory data were presented. Therefore, Schwann cells are very important elements for nerve regeneration but nerve autografts and allografts are not only Schwann cells but more complex biological structures with which, up to now, any type of artificial conduit made of no biological material is not really competitive, even if filled with cells.

(6) COLLAGEN NERVE GUIDES FOR SURGICAL REPAIR OF BRACHIAL PLEXUS INJURY (2)

Ashley WW Jr, Weatherly T, Park TS
J Neurosurg (6 Suppl Pediatrics) (2006) 105:452–456

Information

In some case of birth-related brachial plexus palsy, direct brachial plexus repair provides a good functional motor recovery with minimal orthopedic deformity. Standard brachial plexus repair techniques often involve autologous nerve graft placement and neurotization. The use of autologous graft material provides a good pathway for the outgrowth of damaged nerves but, though safe and relatively uncomplicated, it carries some disadvantages: 1) incidence of

morbidity associated with brachial plexus surgery, in terms of bleeding, infection and scarring, increases; 2) the most common donor sites, sural nerves, are not long enough to provide an adequate graft when repair of the entire brachial plexus is required; 3) this technique, when performed in cases of severe injury, can sometimes yield poor motor recovery.

It has been widely demonstrated that physical continuity is not the only factor involved in successful nerve outgrowth and regeneration; indeed it has been shown that collagen and other extracellular matrix proteins can act as a scaffold, thus enabling direct neurite growth. To improve surgical outcomes and reduce surgical risks associated with autologous nerve graft retrieval and placement, the authors in this study use collagen matrix tubes (Neurogen) in patients who had clinical evidence of a very severe injury that they believed had a low probability of recovering if traditional graft materials were used. The study, the first conducted in humans, is a retrospective analysis of the initial 5 patients who were treated using the tubes. In all 5 patients the brachial plexus injury was severe and extensive neuromas involving the spinal roots and trunk portion of the brachial plexus were noted.

The decision to use a collagen matrix graft was based on the severity of the injury, the size of the gap after removal of the neuroma and the diameters of the proximal and distal stumps. Four of five patients experienced a good recovery, and three exhibited an excellent recovery at 2 years postoperatively, with a mean increase in MSC (motor scale composite) by 69 and 78% at 1 and 2 years, respectively. Joint movement scores improved to range of motion of at least 50% in most patients, and the contractures were usually mild or moderate. The authors attribute the success of their procedure to several factors: 1) using tubes for gaps smaller than 2 cm, whereas larger gaps would result in aberrant growth or a lack of growth; 2) the careful selection of the diameter of the grafts to ensure a good seal and concentration of growth factors in the tube; 3) the inclusion of a 1-mm cuff of both the proximal and distal stumps in the tube, which are the site of growth factor production within the tube and 4) the removal of air from the tubes which ensures a good gel column for neurite growth and diffusion of growth factors. The authors decided to use the Neurogen tubes to treat only the most severe injuries because, until they had proven the viability of such conduit, they wanted to limit the risk that the tubes would not work as well as sural nerve grafts, ultimately reducing the patient chance for optimal recovery.

Analysis

The authors had five patients who had clinical evidence of very severe brachial plexus injury that they believed had a low probability of recovering if traditional graft materials (i.e. nerve autografts) were used.

Therefore, they decided to use in these severe cases something, the collagen matrix tubes (Neurogen), that they hypothesized to offer better probabilities of functional recovery in comparison with nerve autografts, avoiding even the eventual complications associated with harvesting autologous nerves. This assumption, for which an artificial conduit made of biological materials should offer functional results better than nerve autografts, was “a priori” revolutionary in peripheral nerve repair where up to now autologous nerve graft is still

considered the gold standard for nerve repair. "A posteriori" such assumption could seem reinforced by the results consisting in good or excellent functional recovery in four of the five patients with brachial plexus birth injuries with short nerve gaps. Further, these clinical results in humans seem to confirm previous experimental studies. Collagen matrix tubes were used in monkeys to repair the median nerve with short gaps with good clinical and anatomical results; the axonal regeneration was comparable with that obtained after repair with nerve autografts (1).

In this study, patients showed "clinically" severe brachial plexus injury, being the usual candidates to surgical exploration and repair. The used tubes served to bridge short discontinuities 2 cm or smaller. Then, collagen tubes do not still solve the same old problem, i.e. that sural nerves are not long enough to provide an adequate graft when repair of the entire brachial plexus is required. Collagen matrix tubes are a safe alternative to autologous nerve for short-segment (smaller than 2 cm) brachial plexus and perhaps other peripheral nerve repairs.

Synthesis

The first two papers studied in monkeys the effectiveness of nerve allografts used to repair the ulnar nerve and a branch of the facial nerve; the animals were treated with an immunosuppressant only for the first two months after surgery. Eight months after nerve repair, all monkeys exhibited an apparently normal function of both nerves. The clinical results were similar to those obtained with the classic autografts. At the end of the study, six months after withdrawal of the immunosuppressant, an inflammatory reaction was seen around the allograft as an expression of a rejection reaction. The results of these studies were obtained in a limited period of time and then we do not know if a rejection of the allograft might occur later during the course of a normal life span. The problem of the duration of the immunosuppressant therapy needs to be clarified; temporary therapy was associated with signs of allograft partial rejection.

The following three papers studied artificial conduits made of no biological materials and that were filled with one the following cells: Schwann cells, bone marrow stromal cells, and blood-derived CD133+ cells. The bone marrow stromal cells and blood-derived CD133+ cells differentiated in Schwann cells. Whereas Schwann cells are more difficult to obtain in a sufficient number, bone marrow stromal cells and blood-derived CD133+ cells can be isolated easily from bone marrow aspirates and peripheral blood, respectively, and could be applied as an autologous therapeutic agent with no limitations due to ethical or technical problems. The well known importance of Schwann cells in promoting peripheral nerve regeneration was confirmed in these three studies. However, as in other experimental studies with artificial conduits made of no biological material only a minimal part of their cross-section was occupied by nerve regeneration represented by rather poor axonal regeneration in terms of low number and small diameter of the regenerated axons if compared with what is seen using nerve autografts and also nerve allografts. Conclusively, better anatomical results were seen after repair with nerve autografts instead of conduits filled with original or derived Schwann cells. These cells are very important elements for nerve regeneration but nerve autografts and allografts are not only Schwann cells but more complex biological structures with which, up to now, any type of

artificial conduit made of no biological material filled with whatever is not really competitive.

The last paper is a retrospective analysis of surgical outcomes in 5 patients with brachial plexus birth injury treated with an artificial conduit made of biological material, the collagen matrix tube (Neurogen). The conduits were used to bridge short discontinuities 2 cm or smaller. Collagen matrix tubes appeared a safe alternative to autologous nerve for short-segment (smaller than 2 cm) brachial plexus repairs.

At the end of this review, the role of autologous nerve autografts as the gold standard for peripheral nerve repair still remains. Allografts must resolve definitively the problem of rejection and the immunosuppressant therapy. Conduits made of no biological materials filled with the cells cited in the reviewed papers are not competitive with nerve autografts and even with nerve allografts. Collagen matrix conduits seem competitive with nerve autografts for short nerve gaps (less than 2 cm).

References

1. Archibald SJ, Shefner J, Krarup C, Madison RD: Monkey median nerve repaired by nerve graft or collagen nerve guide tube. J Neurosci 15:4109-4123, 1995.

2. Ashley WW, Jr., Weatherly T, Park TS: Collagen nerve guides for surgical repair of brachial plexus birth injury. J Neurosurg 105:452-456, 2006.

3. Auba C, Hontanilla B, Arcocha J, Gorria O: Peripheral nerve regeneration through allografts compared with autografts in FK506-treated monkeys. J Neurosurg 105:602-609, 2006.

4. Hontanilla B, Auba C, Arcocha J, Gorria O: Nerve regeneration through nerve autografts and cold preserved allografts using tacrolimus (FK506) in a facial paralysis model: a topographical and neurophysiological study in monkeys. Neurosurgery 58:768-779; discussion 768-779, 2006.

5. Kijima Y, Ishikawa M, Sunagawa T, Nakanishi K, Kamei N, Yamada K, Tanaka N, Kawamata S, Asahara T, Ochi M: Regeneration of peripheral nerve after transplantation of CD133+ cells derived from human peripheral blood. J Neurosurg 110:758-767, 2009.

6. Mimura T, Dezawa M, Kanno H, Sawada H, Yamamoto I: Peripheral nerve regeneration by transplantation of bone marrow stromal cell-derived Schwann cells in adult rats. J Neurosurg 101:806-812, 2004.

7. Noble J, Munro CA, Prasad VS, Midha R: Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. J Trauma 45:116-122, 1998.

8. Sinis N, Schaller HE, Schulte-Eversum C, Schlosshauer B, Doser M, Dietz K, Rosner H, Muller HW, Haerle M: Nerve regeneration across a 2-cm gap in the rat median nerve using a resorbable nerve conduit filled with Schwann cells. J Neurosurg 103:1067-1076, 2005.

9. Udina E, Gold BG, Navarro X: Comparison of continuous and discontinuous FK506 administration on autograft or allograft repair of sciatic nerve resection. Muscle Nerve 29:812-822, 2004.

10. Yang RK, Lowe JB, 3rd, Sobol JB, Sen SK, Hunter DA, Mackinnon SE: Dose-dependent effects of FK506 on neuroregeneration in a rat model. Plast Reconstr Surg 112:1832-1840, 2003.

Reviewed papers

1. Auba C, Hontanilla B, Arcocha J, Gorria O: Peripheral nerve regeneration through allografts compared with autografts in FK506-treated monkeys. J Neurosurg 105:602-609, 2006.

2. Hontanilla B, Auba C, Arcocha J, Gorria O: Nerve regeneration through nerve autografts and cold preserved allografts using tacrolimus (FK506) in a facial paralysis model: a topographical and neurophysiological study in monkeys. Neurosurgery 58:768-779; discussion 768-779, 2006.

3. Sinis N, Schaller HE, Schulte-Eversum C, Schlosshauer B, Doser M, Dietz K, Rosner H, Muller HW, Haerle M: Nerve regeneration across a 2-cm gap in the rat median nerve using a resorbable nerve conduit filled with Schwann cells. J Neurosurg 103:1067-1076, 2005.

4. Mimura T, Dezawa M, Kanno H, Sawada H, Yamamoto I: Peripheral nerve regeneration by transplantation of bone marrow stromal cell-derived Schwann cells in adult rats. J Neurosurg 101:806-812, 2004.

5. Kijima Y, Ishikawa M, Sunagawa T, Nakanishi K, Kamei N, Yamada K, Tanaka N, Kawamata S, Asahara T, Ochi M: Regeneration of peripheral nerve after transplantation of CD133+ cells derived from human peripheral blood. J Neurosurg 110:758-767, 2009.

6. Ashley WW, Jr., Weatherly T, Park TS: Collagen nerve guides for surgical repair of brachial plexus birth injury. J Neurosurg 105:452-456, 2006.