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REVIEW ARTICLES OF TOPICS

Nerve Allotransplantation as it Pertains to Composite Tissue Transplantation

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Abstract Nerve allografts provide a temporary scaffold for host nerve regeneration and allow for the repair of significant segmental nerve injuries. From rodent, large animal, and nonhuman primate studies, as well as clinical experience, nerve allografts, with the use of immunosuppression, have the capacity to provide equal regeneration and function to that of an autograft. In contrast to solid organ transplantation and composite tissue transfers, nerve allograft transplantation requires only temporary immunosuppression. Furthermore, nerve allograft rejection is difficult to assess, as the nerves are surgically buried and are without an immediate functional endpoint to monitor. In this article, we review what we know about peripheral nerve allograft transplantation from three decades of experience and apply our current understanding of nerve regeneration to the emerging field of composite tissue transplantation.

Keywords Nerve allotransplantation · Composite tissue transplantation · Immunosuppression

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Composite tissue allografting is an exciting field that can drastically change the lives of many individuals plagued with severe injuries. This emerging field takes into account the transplantation and immunology of multiple tissues. Peripheral nerve regeneration is critical for the function and sensation of these transplanted parts whether involving the face or an extremity. In this article, we review what we know about peripheral nerve allotransplantation from three decades of experience and apply our current understanding of nerve regeneration to the field of composite tissue transplantation.

Nerve Allografting

The repair of large, segmental, or complex nerve injuries requires equally long autogenous nerve grafts in which the supply is commonly insufficient for repair. When nerve continuity cannot be restored by a tension-free coaptation and donor autografts are insufficient, cadaveric nerve allografts provide a readily accessible alternative. Transplanted nerve allografts act as a temporary scaffold providing the substrate to permit host axonal regeneration. They also avoid graft site morbidity associated with nerve autografting such as sensory loss, scarring, and neuroma formation. The results of studies on rodent, large animal, and nonhuman primates, as well as clinical experience has demonstrated in the presence of immunosuppression nerve allografts provide equal regeneration and function to that of an autograft. However, due to the risks of temporary systemic immunosuppression (approximately 2 years) and the recent successful use of other autograft alternatives, such as nerve transfers or nerve transfers used in combination with autografting, the indication for nerve allotransplantation is relatively rare. Nerve allotransplantation should be reserved

for unique patients with irreparable peripheral nerve injuries which left untreated would lead to an essentially nonfunctional limb.

In contrast to the allotransplantation of solid organs, nerve allografts require only temporary systemic immunosuppression [38]. Once axon regeneration has crossed the transplanted nerve allograft, systemic immunosuppression can be withdrawn [23, 38]. In organ transplantation, measurements of organ function, such as serum creatinine and liver transaminases, provide clinicians with an objective means to detect rejection. In contrast, rejection of nerve allografts is difficult to assess as the nerves are surgically buried and an immediate functional endpoint does not exist to alert one to rejection. In nerve allotransplantation, once rejection is detected, usually by overlying inflammation or erythema, it is usually too late for the rescue of the graft with modifications of the immunosuppression [1]. Thus, having clinical suspicion and ensuring patient compliance to the immunosuppressive regime is critical.

Nerve Allograft Immunosuppression with FK-506

Extensive and significant research has examined the immunology of nerve allograft transplantation [1, 2, 22, 24, 30, 43]. Previous studies have focused on minimizing the negative side effects of immunosuppression while maximizing nerve regeneration. Nerve allograft transplantation induces both a humoral and cell-mediated immune response [16, 26, 34, 50, 51]. In nerve allografts, Schwann cells (SCs) represent the main immunogenic target for acute and chronic rejection. SCs elicit host immune response through expression of both major histocompatibility complex (MHC) I and II [30, 34, 41, 52, 58].

Our laboratory began investigating the effects of immunosuppression on nerve regeneration and nerve allograft survival in the late 1970s and specifically looked at the calcineurin phosphatase inhibitor, FK-506, in the late 1990s. FK-506, also known as tacrolimus, ultimately inhibits the activation of T-cell proliferation [55]. FK-506 had a significant effect in solid organ transplant immunosuppression when it became approved for clinical use in the early 1990s [18, 42]. Gold et al. was first to describe augmented neuroregeneration provided by FK-506 in peripheral nerves [19]. FK-506 has since been shown to be effective in the enhancement of peripheral nerve regeneration in multiple models including transection [28], crush [31, 54], chronic axotomy [48], isograft [11], and allograft [14, 38] models. Beyond improved nerve regeneration, FK-506 has been shown to accelerate functional recovery in small and large animal models [27, 28]. The immunosuppressive mechanism of FK-506 is mediated through calcineurin-inhibition [8, 32], yet the exact mechanism of its neuroregenerative properties remains unclear. Evidence for calcineurin-independent pathway of action suggests that other mediators, such as FKBP-52, GAP43, heat shock proteins, and cytoskeletal dynamics may be involved [20, 29, 49].

Delays in administration of FK-506 should be avoided [44, 45]. Our clinical and research experience has demonstrated that FK-506 should be administered preoperatively for a greater effect on nerve regeneration and functional recovery. In 2006, we demonstrated that preloading FK-506 3 days before surgery enhanced the neuroregenerative effects of the drug [44]. We further demonstrated that if immunosuppression drops below therapeutic levels and rejection is suspected, the allograft can be rescued by providing immunosuppressive doses of FK-506 but only within 7 days of the start of rejection [14]. These observations have been translated to the senior author's current clinical practice.

In the course of our investigations, we also discovered that low dose FK-506 in combination with other immunosuppressive regimes (anti-CD-40 ligand/co-stimulatory blockade and cold preservation in University of Wisconsin solution) continued to enhance peripheral nerve regeneration [5, 21]. In contrast, immunosuppressive doses of FK-506 with therapeutic doses of anti-CD-40 ligand/co-stimulatory blockade abrogates the beneficial effects of FK-506 on nerve regeneration [5]. Although not specifically studied, we suspect the decreased regenerative enhancement by FK-506 results from interference of each others mechanism of action (co-stimulatory blockade versus calcineurin inhibition), making both drugs less effective. For example, alloantigen needs to be recognized by host T cells to allow costimulation to be effective. Further studies are needed to elucidate the specifics behind this phenomenon.

Clinical Experience

Currently, the senior author has reserved nerve allografting for only devastating injuries which otherwise would not be reconstructable and would lead to total functional limb loss. The introduction of nerve transfers in the last several years has allowed for the treatment of more proximal and extensive nerve injuries, avoiding the need for nerve allotransplantation in some instances [9, 10, 35, 36, 39, 40]. Interestingly, decellularized cadaver nerve allografts are also now available commercially for use in nerve reconstructions. However, their use is limited to the repair of nerve gaps less than 3 cm in length and for small diameter nerves [57]. Experimental and clinical evidence for the use in longer gap lengths has not yet been demonstrated. Thus, we would only recommend the use of decellularized nerve allografts for short defects in small

diameter nerves. Furthermore, while several commercially available synthetic absorbable and nonabsorbable nerve conduits exist, these too are limited by gap length and nerve diameter [6, 7, 37, 47]. Thus, in the event of truly devastating and extensive nerve injuries, the use of nerve allograft transplantation is the only viable and efficacious option.

Our current clinical regimen for nerve allotransplantation consists of using allografts taken from ABO blood-type-matched individuals as well as obvious available donor autografts. Recently, living related donors have been used in addition to cadaveric specimens. In one patient autograft, donor-related and donor-unrelated (noncadaveric) allografts were all used in the repair. We recommend using donor-related nerve allografts whenever possible because it shortens the wait time between the determination of the need for surgery and the actual operation. In our experience, a waiting period of 2–3 months to obtain cadaver nerves exists due to the current national system of tissue procurements.

In addition to the blood type compatibility, multiple small diameter nerves are used in contrast to larger diameter nerves to avoid necrosis of the central aspect of the nerve from lack of adequate revascularization. The allografts then undergo cold preservation in University of Wisconsin solution with antibiotics at 4°C for 7 days prior to implantation to decrease immunogenicity [13, 46]. Preoperatively, FK-506 is given to the patient 3 days prior to surgery for induction and to maximize the regenerative effects of the drug. Our current immunosuppressive drugs include the use of FK-506 and azathioprine. Our patient protocol is illustrated in Table 1.

The senior author has published her cases of human nerve allotransplantation (for review see [38]). Since 1988, 11 patients have been treated with a combination of autografts and donor allografts. In the two most recent patients, living related donors have been used in addition to cadaveric specimens. In one patient, autograft, donor-related and donor-unrelated (noncadaveric) allografts were all used in the repair. Ten of the 11 patients have had a good recovery, while a single patient developed rejection following subtherapeutic dosing with FK506.

Schwann Cell Migration

Host SC migration is essential for nerve allograft survival and axonal regeneration through the graft. In order to minimize immunosuppressive therapy, both host and donor SC migration and viability are critical. Studies exploring SC behavior and migration have demonstrated that host SCs migrate into the nerve allograft from both proximal and distal host nerve ends (Fig. 1) [15, 17, 27, 53]. Observations of in vivo imaging show that there appears to be more migration from the distal host nerve. Host SCs repopulate an accellularized graft proximal and distally very early (within 10 days) and axonal regeneration lags behind SC migration by 10–15 days [27].

Table 1 Nerve allotransplantation patient protocol.

Preoperative preparation	Intraoperative details	Postoperative care
Assess patient suitability Medical comorbidities Infection/malignancy Psychosocial fitness	Resect patient's injured nerve to healthy proximal and distal stumps	Induction immunotherapy (dose 2) Basiliximab 20 mg intravenously (postoperative day 4)
Laboratory tests ABO blood type CBC, CMP HIV/hepatitis	Use patient's autografts in addition to cadaveric allografts, donor-related or donor-unrelated allografts	Standard immunotherapy continue FK-506 (goal level 5–8 ng/ml) Azathioprine 1–1.5 mg/kg/day
Nerve allografts Consider related donor Harvest small diameter grafts Cold preservation (4°C, University of Wisconsin solution, 7 days	Insert extra allograft subcutaneously for rejection monitoring	Antibiotics Sulfamethoxazole-trimethoprim Three times a week
Immunotherapy FK-506 (tacrolimus) 1–2 mg by mouth B. I.D. (start 3 days preoperatively) Induction immunotherapy (dose 1)—Basiliximab 20 mg intravenously (immediately preoperatively)		Stop immunotherapy 6 months after Tinels crosses distal repair site

Modified from I. K. Fox and S. E. Mackinnon. Seminars in Plastics Surgery/Vol 21, Number 4 2007 [13]

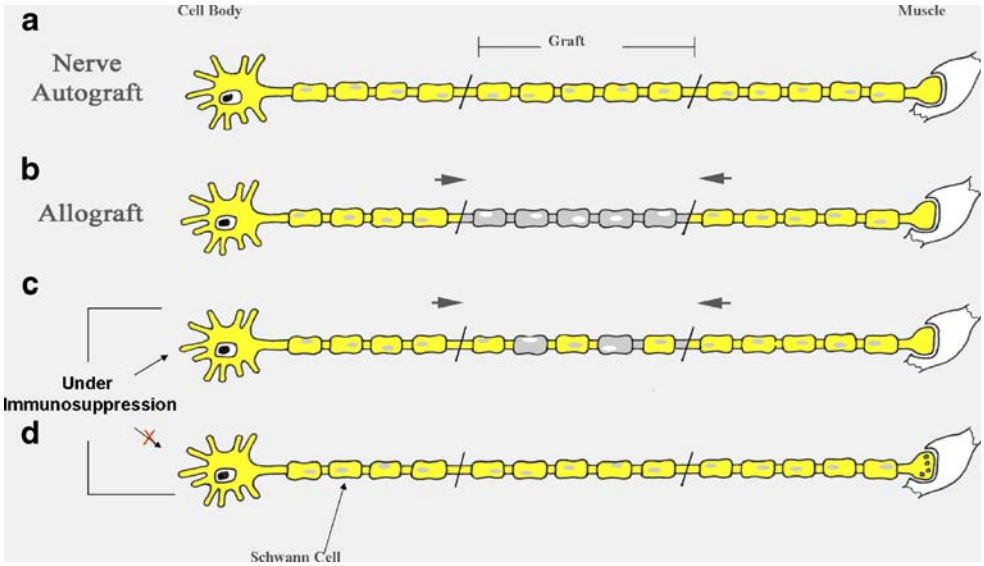

Figure 1 Schwann cell migration. In the nerve autograft (**a**), Schwann cells (SCs) in the graft support the survival. **b** In the nerve allograft, host Schwann cells (SCs) migrate from both proximal and distal host nerve into the donor graft. **c** Under adequate immunosuppression, the host SCs coexist with donor SCs within the allograft and support axonal regeneration through the graft. **d** Once immunosuppression is stopped, the host SCs migrate across the entire graft and replace the donor SCs.

Recent studies in our laboratory have further explored SC migration into a nerve allograft. We determined that under adequate immunosuppression there is a delay in host SC migration across the entire graft. During this delay, the donor SCs appear to assist axonal regeneration across the graft. [56]. Over time, host SCs migrate into the graft and both host and donor SCs coexist. This movement of host SCs across the graft may be related to episodes of subclinical rejection because once immunosuppression is stopped, we immediately see host SC migration into graft [56]. These findings shed insight into the support and survival of nerve allografts by SCs and become inherently important when considering the survival of nerves in composite tissue transplantation.

Nerves in Composite Tissue Allotransplantation

Composite tissue allografts represent a unique challenge for long-term nerve allograft viability. Ultimately, the long-term functional outcome in patients undergoing either hand or face transplantation requires appropriate and sufficient nerve regeneration. Neuromuscular recovery as well as sensory function have been described in both small animal models [3, 4] and primate models [12, 25] undergoing composite tissue transfers. More recently, Cottrell et al. observed fewer axons with a higher percentage of myelination in transplanted nerves in rats undergoing hind limb transplantation. In nerve allotransplantation, allograft survival largely depends upon both proximal and distal SC

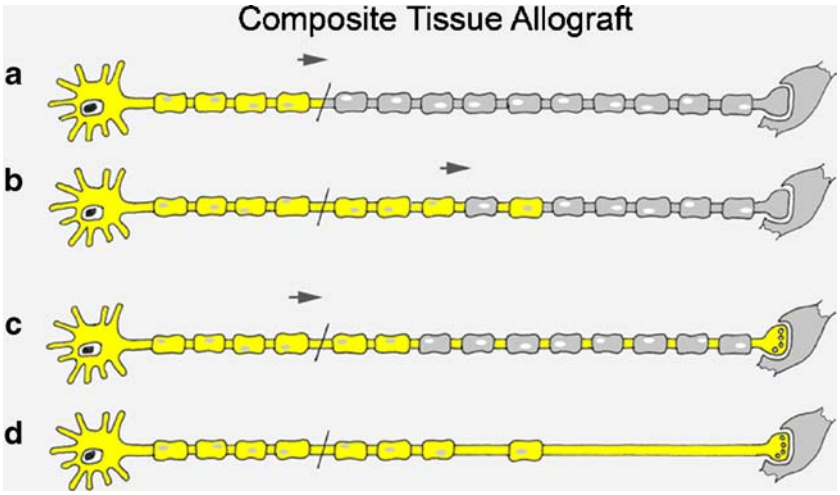

Figure 2 Schwann cell migration in composite tissue allotransplantation. **a** In the composite tissue transplanted nerve, there are no distal host Schwann cells (SC). **b** SC migration occurs only from proximal end. **c** With adequate immunosuppression, both host and donor SCs will support axonal regeneration and allow for end organ reinnervation. **d** If episodes of rejection occur and donor SCs are lost, neurapraxia may ensue and potentially a complete and permanent conduction block may occur resulting in no return of function.

migration during axonal regeneration with end-organ function dependent upon autologous axonal regeneration. However, in composite tissue allotransplantion, critical distal host SCs do not exist. Thus, is the observed restoration of function and robust myelination found in composite grafts due solely to migrating host SCs or are donor SCs responsible for myelination and return of function? Or is host uninjured neuromuscular function proximal to the composite tissue allograft responsible for return of function? Will host SCs migrate to encompass the entire nerve in the environment of long-term immunosuppression?

The answers to the behavior of host and donor SC migration in composite tissue allotransplantation have not yet been elucidated. Our current research is directed at exploring specifically nerve regeneration and the influence of SCs in limb allotransplantation. However, from our understanding of nerve allotransplantation, we believe that the nerves in composite tissue transfers need perfect SC support for regeneration. This may require no lapses in immunosuppression to prevent loss of the donor SCs. Without the migration of distal host SCs, donor SCs are critical for the axonal regeneration and end-organ function. If the nerve is demyelinated distally with loss of distal SCs, then neurapraxia and potentially complete and permanent conduction block may occur resulting in permanent functional loss [33] (Fig. 2). Thus, effective immunosuppression and the avoidance of rejection are critical for the survival of donor SCs and the ultimate survival and function of the composite tissue transplant.

Conclusion

Adequate neural regeneration and end-organ function is critical for composite tissue allotransplantation function. Unfortunately, there are many unanswered questions still remaining. Understanding the history and experience with nerve allotransplantation, as well as, future work focusing specifically on the impact of SC migration and neural regeneration is necessary to improve outcomes.

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