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General

Vascularized Nerve Grafts: Current Concepts, Indications, and Future Perspectives

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Peripheral nerve injuries pose significant challenges due to limited regenerative capacity and functional recovery, especially in large or complex defects. Traditional repair methods using non-vascularized autologous nerve grafts often result in suboptimal outcomes due to ischemia-induced central necrosis and delayed axonal regeneration. Vascularized nerve grafts (VNGs), which provide an intrinsic blood supply, have emerged as a promising alternative to enhance nerve repair by improving graft survival, supporting Schwann cell viability, and promoting early neovascularization.

This review on vascularized nerve grafting examines its advantages, challenges, and emerging experimental approaches. VNGs demonstrate superior functional outcomes compared to non-vascularized grafts, with improved motor and sensory recovery, and higher axonal density, particularly in long-gap and delayed repairs. Although the use of vascularized nerve grafts is limited by technical complexity, increased operative time, and donor site morbidity.

In this study we aim to provide a comprehensive overview of the rationale, outcomes, and challenges associated with vascularized nerve grafts, while highlighting emerging experimental strategies poised to overcome current limitations in peripheral nerve repair.

INTRODUCTION

Severe motor and sensory impairments are frequently the consequence of peripheral nerve injuries. Nerve grafting is necessary to fill in gaps when direct repair is not feasible. Autografts and other non-vascularized nerve grafts (NVNGs) continue to be the clinical standard because of their structural compatibility. However, NVNGs are constrained by slow and frequently insufficient revascularization particularly in ischemic beds, long defects or poorly repaired injuries. This results in compromised axonal regeneration, Schwann cell death and central graft necrosis. Vascularized nerve grafts (VNGs) were created to address these problems. Through microsurgical anastomosis, VNGs provide a direct blood supply, improve oxygenation and hasten axonal growth while maintaining Schwann cell viability. Comparing VNGs to NVNGs, numerous studies demonstrate that the former produce better motor and sensory outcomes, higher axonal density, better myelination and improved electrophysiological parameters. Scarred beds, irradiated fields, delayed reconstruction and gaps larger than 6 cm are the difficult situations where these advantages are most noticeable. VNGs are technically challenging, they necessitate microsurgical skills and are linked to longer operating times and donor site morbidity despite these benefits. In order to replicate the benefits of VNGs while minimizing their limitations, research has resorted to tissue-engineered VNGs and biomimetic scaffolds. New approaches include angiogenic factor-embedded biodegradable conduits, platelet-rich plasma (PRP), stem cell treatments and prefabricated vascularized scaffolds.

1. HISTORICAL MILESTONES IN VASCULARIZED NERVE GRAFTING

The concept of nerve vascularity has evolved over more than a century. Phillipeaux and Vulpian performed the first ever nerve graft in 1870.[1] The first VNG in the upper extremity was a pedicled graft, described by Frederick St Clair Strange in 1947.[2] He used a 12 centimetre (cm) pedicled ulnar nerve graft to repair a 12 cm median nerve gap. The most innovative step was taken in 1976 when Ian Taylor and Ham reported the first free VNG, using a 24 cm segment of the superficial radial nerve based on the radial artery in order to reconstruct a gap in the median nerve in a patient with Volkmann's Ischemic contracture.[3] These pio-

neering efforts laid the foundation for modern microsurgical nerve reconstruction techniques.

2. ANATOMY AND PHYSIOLOGY OF NERVE HEALING

The importance of an adequate and sustained vascular supply to peripheral nerves is a foundational principle that underlies the efficacy of VNGs in reconstructive surgery. Historical investigations into the vascularity of peripheral nerves dates back to the 1970s establishing the critical importance of both extrinsic and intrinsic vasculatures of peripheral nerves.[4] Peripheral nerves have a complex vascular network. The extrinsic supply is derived from surrounding vessels that anastomose to form a longitudinal vasa nervorum on the epineurium. Whereas the intrinsic supply comprises arterioles, capillaries, and venules that penetrate the fascicles.[5] The abundant epineural vascular plexus supplies the endoneural capillaries, which to note are significantly larger than those observed in other tissues.[6] The extrinsic supply consists of segmental arterioles originating from major arterial trunks within adjacent soft tissue which in turn feed a comprehensive network of vessels. From this superficial plexus, small branches penetrate the epineurium at regular intervals reaching individual fascicles enveloped by perineurium and ultimately supplying the endoneurium where Schwann cells and axons reside. This vascular system ensures robust perfusion facilitating the delivery of oxygen and nutrients while removing metabolic waste.[6]

The blood flow in nerve regeneration is of significant importance, as perfusion directly supports the elevated metabolic demands of regenerating axons, Schwann cells, and fibroblasts through the phases of Wallerian degeneration and subsequent axonal regeneration.[7] An adequate blood supply facilitates the transport of neurotrophic factors such as nerve growth factor and growth promoting cytokines to the injury site. The combination of these molecules are essential for guiding axonal sprouting, promoting effective remyelination, and preserving the structural integrity of newly formed nerve tissue.[8] It is extensively documented in the literature that angiogenesis plays an intimate role in the reinnervation, arborization, and growth of peripheral nerves with vascularization preceding the process of innervation.[9] After peripheral nerve damage, the diameter of blood vessels within the intraneural vascular system characteristically increases. This vasodilation is associated with the release of chemoattractants by Schwann cells promoting macrophage recruitment. Migrating and resident macrophages secrete vascular endothelial growth factor (VEGF) stimulating neoangiogenesis.[8] The complex molecular interaction among the above mentioned cells represents a critical area of ongoing investigation and research.

Compromised vascularity represents a primary mechanism of ischemia related failure. This condition is particularly prevalent in long nerve gaps or segments situated in highly scarred recipient beds.[6] In absence of sufficient blood flow, the injured nerve segment can quickly succumb to hypoxia and nutrient deprivation leading to possibly irreversible axonal degeneration.[10] Overall, complete nerve ischemia can precipitate conduction failure in a relatively short period of time, typically 25-30 minutes, whereas permanent axonal damage may necessitate a longer period varying between 1 and 3 hours.[6] In diabetic nerves however, damage ensues more rapidly and extensively under ischemic conditions.[6] The sequential morphological changes that takes place during ischemic events has been described by Nukada and colleagues in human nerve biopsies. Ischemic environments establish a deleterious milieu for regenerating axons, frequently resulting in proximal neuroma formation and persistent distal deficits posing significant challenges to functional restoration.[11]

3. MECHANISM OF REVASCULARIZATION OF NERVE GRAFTS

The revascularization of nerve grafts is one of the main determining factors for survivability and regenerative capacity, particularly given the high metabolic demand. This process unfolds depending on the graft type. In NVNG, revascularization is achieved via two pathways: inosculation and centripedal neovascularization.[12] Inosculation involves the direct connection of host vessels from the recipient bed with the existing vessels in the graft. Historically, this process was thought to occur from both ends of the graft, however Chalfoun et al performed a rat study in 2003 that showed proximal vascular growth advancement was favored over bidirectional advancement.[13]Concurrently, centripetal neovascularization contributes by the ingrowth of new capillaries from the surrounding recipient tissue into the graft. This reliance on secondary vascularization means that NVNG typically require 7 to 10 days for complete perfusion. This period makes the graft susceptible to ischemia, which may lead to Schwann cell death and increased fibroblast infiltration especially in longer or compromised recipient beds.[12,14] In contrast, VNG circumvent this ischemic delay by maintaining immediate and continuous circulation through their preserved vascular pedicles. This inherent vascularity ensures a continuous supply of oxygen and nutrients preserving the viability of crucial cellular components.[14]

4. CLASSIFICATION OF VNGS

The foundational classification of nerves based on vascular supply was introduced by Taylor and Ham in 1976, and was based on the anatomical properties of the graft and was divided into 5 categories[3]:

- Type A: Single dominant vessel
- Type B: Multiple segmental vessels
- Type C: Perineural vascular plexus
- Type D: Combination of the above
- Type E: Perforator-based blood supply

Terzis and Breidenbach conducted a comprehensive cadaveric study of 13 nerves and identified six with sufficient intrinsic blood supply as ideal candidates for vascularized

nerve grafts, proposing new classification criteria and a method for forming vascularized cable grafts.[15]

Three types were determined of which type I was the most effective:

- Type I: Single dominant artery
- Type II: Multiple arteries over the length
- Type III: Random pattern of small vessels

More recently, El-Barrany and colleagues contributed valuable clinical evidence supporting the superiority of VNGs in specific contexts, highlighting enhanced axonal regeneration and functional outcomes. In their research they divided the types of blood supply that a traversing nerve receives into 5 types[16]:

- I: no dominant arterial pedicle
- II: only one dominant artery (amenable to microvascular anastomosis)
- III: only one dominant vessel that is divided into ascending and descending branches to supply the nerve
- IV: multiple dominant pedicles
- V: multiple dominant arterial pedicles forming a continuous artery that accompanied the nerve.

5. VASCULARIZED VS NON-VASCULARIZED NERVE GRAFTS

A. DEFINITIONS AND PHYSIOLOGICAL DIFFERENCES

As previously mentioned, NVNGs are nerve segments harvested without preservation of their intrinsic blood supply. Therefore, revascularization begins around 48 to 72 hours postoperatively from harvesting and is completed by 7 to 10 days.[12,17]

In contrast, VNG maintain their original blood supply through a vascular pedicle which is harvested and preserved and then anastomosed to vessels in the recipient bed. This results in immediate perfusion.[12,14]

B. HARVESTING TECHNIQUES

I. NVNGS

The sural nerve is frequently chosen for this purpose due to its considerable length and minimal donor-site morbidity.[18] Traditional harvesting methods required extensive incisions, leading to increased postoperative complications.[19] Innovative approaches now focus on minimally invasive techniques to mitigate these issues.[18]

On the other hand, for shorter nerve gaps, other donor nerves are considered. Harvested from the medial aspect of the arm, the medial antebrachial cutaneous nerve (MABC nerve) provides grafts suitable for upper extremity nerve reconstructions. It branches into anterior and posterior divisions, allowing for selective harvesting based on the required length and diameter, but the anterior branch is often preferred to minimize sensory deficits over the elbow.[20,21] Furthermore, the greater auricular nerve (GAN) originates from the cervical plexus and is commonly used for reconstructing injured facial nerves. However, care must be taken to avoid sensory deficits in the areas it innervates, such as parts of the auricle and skin over the parotid gland.[22]

II. VNGS

The harvesting of VNGs necessitates advanced microsurgical skills and a thorough understanding of the donor nerve's vascular anatomy. To begin with, the sural nerve can be harvested as a vascularized graft by preserving its association with specific vascular branches. However, studies have shown that in two-thirds of cases, the sural nerve lacks a dominant arterial pedicle, making it less reliable for vascularized grafting in some individuals.[16] Alternatively, the sural nerve may be supplied by branches from the posterior tibial artery, offering another potential vascular pedicle for grafting.

On the other hand, the ulnar nerve, which is supplied by the superior ulnar collateral artery (SUCA), serves as a viable option for vascularized grafting, especially when it is irreparably damaged. It supplies blood along the course of the nerve, which allows for the harvesting of the ulnar nerve as a vascularized graft, particularly beneficial in reconstructing significant nerve defects in the upper extremity.[23]

Furthermore, the superficial branch of the radial nerve and the lateral femoral cutaneous nerve have been identified as potential donors for vascularized nerve grafting.[16,24]

C. ANIMAL STUDIES AND CLINICAL EVIDENCE

Animal studies have consistently demonstrated the histological and electrophysiological advantages of VNGs over NVNG. Broeren et al. conducted a meta-analysis of 14 animal studies, revealing that VNG resulted in significantly larger nerve fiber diameters, higher nerve conduction velocities, and increased axon counts compared to NVNG.[14] Furthermore, Zhu et al. utilized a rabbit facial nerve model to compare VNG and NVNG. Their findings indicated significantly better axonal regeneration and functional recovery on the VNG side, suggesting the superiority of VNGs in facial nerve repair.[25]

In addition, Giglia et al. examined VNG and NVNG in a rat sciatic nerve model. They observed a higher motor unit number estimation (MUNE) in the VNG group, although there was no significant difference in myelinated fiber count or axon diameter between the groups.[26] Saffari et al. investigated the impact of surgical angiogenesis on decellularized nerve allografts in a rat sciatic nerve defect model.[27] By wrapping the allografts with a pedicled adipofascial flap to enhance vascularization, they observed a significant increase in vascularity within the nerve graft and improved early muscle force recovery compared to allografts without the vascularized flap. This suggests that providing blood to grafts can reduce ischemic time, minimize intraneural fibrosis, and create a better environment for nerve regeneration, particularly in scarred or poorly vascularized beds.

Clinical data on VNG remain less extensive than animal studies but provide important insights regarding their indications and outcomes. D'Arpa et al. conducted a meta-

analysis of 95 studies, and showed that VNGs possess a clear advantage and superiority in gaps of more than 6cm, delayed repairs, proximal lesions in nerves and larger nerve diameters.[28]

6. INDICATIONS FOR VASCULARIZED NERVE GRAFTS

When a nerve gap exceeds roughly 6 cm, the central portion of a NVNGs is at high risk of ischemia and cell death. VNGs preserve their own intrinsic blood supply, ensuring uniform perfusion, Schwann cell viability, and enhanced axonal regeneration.[12,29] In tissues compromised by previous trauma, radiation, or extensive scarring, host tissue cannot reliably revascularize a NVNG. In contrast, VNGs introduce a dedicated vascular pedicle, overcoming hostile graft beds and markedly reducing the risk of central necrosis.[30, 31] Moreover, Failed primary grafts often result from fibrosis and poor revascularization. Revision with a VNG provides immediate and sustained blood flow, facilitating axonal growth in an otherwise inhospitable environment.[30,32] Reconstruction of high-value motor or mixed nerves (e.g., brachial plexus, median nerve) demands rapid, high-quality reinnervation. Both animal models and clinical series demonstrate superior motor end-plate reinnervation, faster conduction velocities, and better functional outcomes with VNGs compared to NVNGs.[14,33] Younger patients exhibit heightened regenerative potential. In this population, VNGs capitalize on that biologic advantage, yielding near-complete motor (≥ M4) and sensory recovery even in extensive or proximal defects.[30,34] In fact, Chronic neuroma pain arises from disorganized axonal sprouting and scar formation. Resecting the neuroma and interposing a VNG promotes orderly nerve regeneration, with durable pain relief and restoration of sensibility.[35,36] Traumatic or oncologic resections may necessitate both nerve continuity restoration and soft-tissue coverage. Neurovascular flaps— such as the superficial circumflex iliac artery perforator (SCIP) or the anterolateral thigh (ALT) flaps incorporating a vascularized nerve segment —simultaneously provide durable tissue coverage and a perfused conduit for axonal growth.[30, 35] In summary, the indications for VNGs include: large nerve defects (>6cm), scarred/irradiated/ or ischemic recipient beds, revision nerve reconstructions, reconstruction of critical motor or mixed nerves, pediatric and young adult patients, painful neuromas/neuroma-in-continuity, and composite soft tissue/ nerve defects.

7. SURGICAL TECHNIQUES AND DONOR SITES

In a review published by Terzis and Kostopoulos, where the most commonly used VNGs were analyzed, the authors concluded that the ideal graft would have one dominant vessel running for most of its length, i.e. a type 2 pedicle in the Breidenbach and Terzis classification.[15,37]

With this in mind, several vascularized nerve grafts and multiple nerve donors have been described in the literature. Techniques include[37]:

- Pedicled vascularized nerve grafts
- Free vascularized nerve grafts
- Arterialized nerve grafts
- Arterialized venous fistula nerve grafts
- Arterialized venous grafts

With free VNGs, a nerve graft is transferred with in conjunction with its artery and vein, the direction of blood flow being as follows: recipient artery to artery of the graft to capillaries to vein of the graft to recipient vein. Anastomoses with the recipient vessels in these grafts are usually end to side, but they can also be side to side. Arterialized nerve grafts consist of a free VNG transferred with only its associated artery. In these grafts, blood flows from the recipient artery into the dominant artery of the graft and then into the distal recipient vein. Arterialized venous fistula nerve grafts involve the transfer of a nerve graft with an associated vein. In these grafts, blood flow is directed from the recipient artery to the graft-associated vein and then into the recipient vein. Arterialized venous nerve graft consists of transferring a nerve graft with its vein and directing blood flow from the recipient artery to the graft vein and then into the recipient artery.[36] It is important to remember that these techniques are feasible because the metabolic demands of the nerve graft are relatively low. This allows the use of venous anastomosis alone to sustain the vascularity of the transferred nerve graft.

The sural nerve is typically harvested as a free VNG based on the superficial sural artery or along with an arterialized venous nerve graft when transferred along with the lesser saphenous vein. It can be used as a pedicled VNG for lower extremity reconstructions or as a free VNG for upper extremity reconstructions.[30,37]

The saphenous nerve has also been used as a VNG due to its excellent length, expendable nature and anterior location, however its dissection is extensive since exposure of the Hunter canal is needed.[15,38] It has multiple dominant pedicles, being supplied by the femoral vessels proximally and the saphenous vessels in the lower thigh and knee.[14,39]

The ulnar nerve has been extensively studied in the context of both pedicled and free VNGs, mainly due to its multiple dominant blood supply (type 3 Breidenbach and Terzis blood supply).

Free vascularized ulnar nerve grafts were first introduced by Terzis in 1984 and these were based on the SUCA in the arm for lower brachial plexus avulsions, and since then it has been routinely used to bridge long gaps during plexus reconstruction in cases of global plexopathies with C8-T1 avulsions.[39]

The lateral antebrachial cutaneous nerve has also been described as a VNG option, with Boorman and Sykes publishing a case report where a patient required reconstruction of the two digital nerves in their thumb in whom two lengths of 5cm of lateral antebrachial cutaneous nerve were used (one vascularized, one nonvascularized), with comparison of sensory recovery of the two nerves revealing better sensory recovery at 9 months on the VNG side.[40]

Mackinnon et al described a superficial radial nerve VNG where they used it along with a conventional sural nerve

graft to perform a two-stage median nerve reconstruction and found superior sensory function on the VNG side.[41]

It should be noted that several technical factors need to be considered when performing a nerve graft[42]:

The most essential for any microsurgical anastomosis is to have a tension-free repair. The diameter of the nerve graft should correlate exactly with the proximal and distal ends of the recipient nerve or as close as possible. The number and size of fascicles are also important factors, as well as the fascicular patterns of the donor and recipient nerves and the cross-sectional shape of the nerves (whether the nerve is flat or oval/round). Also, the local vascular environment plays a role, which is one of the reasons VNGs are indicated in areas with scarred recipient bed. Added to that, the graft should be oriented in the same functional direction as which is was harvested: the proximal end of the graft should be anastomosed at the proximal end of the recipient to maintain axonoplasmic flow. A general rule of thumb is that shorter grafts yield better results due to the amount of time for regeneration to occur at each nervous anastomosis (7-14 days) and across the length of the nerve (0.1mm/day). As for the quality of the repair, current recommendations include using 8-0 to 11-0 monofilament nylon sutures with as little sutures as possible (optimally 3-6 simple interrupted sutures) and an accurate approximation of the stumps, while also ensuring that sutures are only epineural and do not pass through the fascicles. It is necessary to point out that a harvested nerve shrinks in length by approximately 20% when cut as it tends to retract, therefore the harvested nerve should be 25% longer than the nerve defect to compensate for these changes.

8. OUTCOMES OF VASCULARIZED NERVE GRAFTING

A. FUNCTIONAL RESULTS

Multiple studies have shown that VNGs lead to improved motor and sensory recovery, particularly in long-gap or scarred beds.[41,43] Faster reinnervation has been consistently observed in animal and human models, attributed to better preservation of Schwann cells and endoneurial architecture.[3,41,43] Electrophysiological assessments report significantly higher compound muscle action potentials and faster conduction velocities in VNGs compared to NVNGs.[44,45]

B. HISTOLOGICAL OUTCOMES

Histological analyses reveal increased axonal density and more uniform myelination in VNGs, suggesting enhanced axonal regeneration. Moreover, VNGs exhibit superior neovascularization, which supports graft viability and nutrient delivery, particularly in ischemic or irradiated environments.[3,43]

C. COMPARATIVE STUDIES

Systematic reviews and meta-analyses consistently demonstrate that VNGs outperform NVNGs in complex reconstructions and extensive defects, reinforcing their value in selected clinical scenarios.[44-46] A 2024 systematic review combining 34 preclinical and 7 clinical studies showed 90% of clinical reports favored VNGs for sensory recovery and 56% for motor function.[47] Yamaguchi University's RCT reported better outcomes with VNGs in grafts >6 cm or when soft tissue coverage was limited.[48] These findings underscore the value of VNGs in long-gap, ischemic, or scarred beds, even though some metrics like muscle reinnervation remain debatable.

9. CHALLENGES AND LIMITATIONS

A. TECHNICAL DEMANDS AND OPERATIVE TIME

Although VNGs have the potential to improve outcomes in nerve reconstruction after injury, the procedures are technically demanding and require microsurgical expertise, particularly in performing vascular anastomosis and identifying suitable recipient vessel. This technical complexity not only increases operative time but also raises the risk of intraoperative complications such as thrombosis, graft failure and vascular insufficiency.[12] A steep learning curve and the need for highly specialized equipment further restrict the procedure to select centers with advanced reconstructive microsurgery capabilities.[49]

B. DONOR SITE MORBIDITY

Clinical application also requires careful consideration of donor site selection and associated morbidity, as both the availability of adequate peripheral nerve tissue and the characteristics of the injury site constrain grafting options.[12] Common donor nerves such as the sural, superficial radial, or lateral femoral cutaneous nerves are often sacrificed, potentially resulting in sensory deficits or neuroma formation.[50] Furthermore, the need to preserve vascular integrity during harvest can lead to more extensive dissection and associated complications. This compromise between functional recovery at the recipient site and morbidity at the donor site remains a critical consideration.[51]

C. LIMITED AVAILABILITY OF HIGH-LEVEL EVIDENCE

Although several case reports and small cohort studies suggest improved axonal regeneration and functional outcomes with VNGs, high-level evidence remains sparse.[52] There is a lack of large-scale, randomized controlled trials directly comparing VNGs with NVNGs across various injury patterns and clinical settings. Heterogeneity in surgical techniques, outcome measures, and follow-up durations further complicates the interpretation of existing data.[53] This limits the ability to make definitive, evidence-based recommendations for VNGs use

D. COST-EFFECTIVENESS CONCERNS

Peripheral nerve injuries are a debilitating condition with significant associated morbidity and which places a substantial socioeconomic burden on healthcare systems worldwide. VNGs, while promising, raise concerns regarding cost-effectiveness due to the increased technical requirements, longer operative times, and potential for prolonged hospital stays. In healthcare systems with finite resources, the economic burden must be weighed against potential functional gains.[54] Few studies have rigorously evaluated the cost-benefit ratio of VNGs, making it difficult to justify their routine use without clearer data demonstrating superior long-term outcomes

10. EXPERIMENTAL AND EMERGING APPROACHES

The repair of injured nerves or tissues often relies on autograft transplantation, widely regarded as the gold standard. Despite their effectiveness, autografts come with notable drawbacks, including possible complications at the donor site and less-than-optimal functional outcomes. Additionally, they may not be suitable for treating large or complex injuries. As an alternative, allogenic grafts can be used, but they typically necessitate lifelong immunosuppressive therapy to prevent rejection and still frequently lead to subpar regeneration. In contrast, tissue engineering offers promising solutions to address these challenges. It relies on a foundational trio: cells, biomaterials, and external cues such as growth factors or physical and chemical signals.[55] Tissue engineering has increasingly aimed to develop grafts that closely mimic natural tissue by integrating both neural and vascular components. These engineered constructs are intended to simulate the native nerve's structure, function, and mechanical characteristics while promoting early blood vessel formation to facilitate axonal repair. Recent findings suggest that in vitro cellular triboelectric nanogenerators seeded with fibroblasts, Schwann cells, and vascular endothelial cells, may facilitate swift integration with the host's vascular network following implantation.[56]

To address ischemic failure in long nerve gaps or compromised beds, researchers have developed vascularized nerve conduits composed of biodegradable materials. An emerging and highly promising approach involves the use of scaffolds embedded with angiogenesis-stimulating biofactors, eliminating the need for incorporating living cells.[57] Vascularized biogenic nerve conduits can be created through a prefabrication process, where an artificial tube is positioned adjacent to a donor nerve or vascular source. Over the course of 1 to 3 weeks, a pseudosheath forms around the conduit. Once formed, the artificial tube is carefully removed, leaving behind the vascularized pseudosheath, which serves as a biogenic nerve conduit. This conduit can be applied directly, combined with biomaterials, or integrated with a nerve graft for therapeutic use.[58]

Researchers have identified numerous bioactive molecules that support blood vessel formation for use in creating vascularized scaffolds. Among these, VEGF stands out as the most extensively studied due to its strong ability to promote angiogenesis. VEGF enhances endothelial cell movement by interacting with neuropilin 1, thereby increasing the scaffold's vascularization potential. Laminin, an extracellular matrix protein known for its beneficial effect on cell proliferation, is frequently used to coat scaffolds to enhance cell interaction during seeding.[57]

Ma et al. investigated the use of natural neural scaffolds made from collagen tubes filled with a targeted delivery system composed of Ordered Collagen Fibers, Collagen-Binding Domains, and VEGF to repair sciatic nerve defects in adult rats. The results demonstrated that these scaffolds supported robust nerve regeneration, with both structural and functional recovery comparable to that achieved with autografts. These findings suggest that such natural neural scaffolds could serve as a promising therapeutic option for peripheral nerve repair.[59]

In their 2022 study, Yadav et al. demonstrated that treatment with platelet-rich growth factors (PRGF) significantly decreased the presence of pro-inflammatory M1 macrophages while encouraging a shift toward the anti-inflammatory M2 phenotype. By influencing macrophage behavior, PRGF effectively altered the local inflammatory response at the injury site, helping to reduce inflammation and promote tissue repair.[60]

PRP is widely used in regenerative medicine due to its composition, which includes elevated levels of platelets, growth factors, white blood cells, fibrin, and bioactive molecules such as fibronectin, osteonectin, and vitronectin. These elements play essential roles in the repair process. Platelet activation not only helps control bleeding but also triggers the release of growth factors that influence multiple stages of tissue regeneration.[56] Additionally, white blood cells assist in clearing infections and removing dead tissue, while fibrin forms a three-dimensional matrix at the injury site, serving as a structural scaffold to support new tissue growth.[61]

Moreover, various types of stem cells, including embryonic stem cells, neural stem cells, and mesenchymal stem cells (MSCs), have shown potential in promoting nerve regeneration. Their benefits are attributed to their ability to differentiate into Schwann-like cells, secrete neurotrophic factors, and support myelin formation. Stem cells can also enhance angiogenesis by secreting angiogenic factors, thus improving blood supply and supporting nerve repair.[62] Besides, exosomes which are extracellular vesicles released by stem cells, play a vital role in cell-to-cell communication. They carry proteins, lipids, and nucleic acids that can modulate the immune response, promote angiogenesis, and support nerve regeneration. The integration of stem cell therapy and strategies to enhance vascularization holds promise for improving outcomes in peripheral nerves injury treatment. However, further research is needed to fully understand the mechanisms of interaction between stem cells and vascularity and to optimize therapeutic approaches.[62]

CONCLUSION

VNGs have been shown to be clinically superior to NVNGs according to available data, particularly in long-gap repairs delayed reconstructions and scarred or ischemic beds—areas where NVNGs frequently fall short. These results have increased the use of VNGs in high-demand reconstructions like brachial plexus repairs and complex peripheral nerve injuries. However, meticulous patient selection is required due to the technical complexity, longer operating time and donor site morbidity linked to VNGs. Large-scale carefully planned randomized controlled trials are desperately needed to elucidate the precise indications, long-term advantages and cost-effectiveness of VNGs in comparison to NVNGs. Advances in biomaterials stem cell therapies, angiogenic scaffolds and bioactive molecules like VEGF and PRP hold promise for enhancing graft viability and functional recovery. Consequently, a new era of individualized successful nerve repair techniques may be ushered in by fusing innovative bioengineering techniques with surgical precision.

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