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Advances in lower extremity peripheral nerve surgery

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Abstract

Peripheral nerve injury (PNI) is a common source of pain and disability in patients. While many patients are affected by PNI, peripheral nerve surgery advancements in the lower extremity have lagged behind the upper extremity. Subsequently, principles that have demonstrated success in the upper extremity have been implemented in the lower extremity. Interventions with recent advances include the advent of novel nerve transfers in the lower extremity and using stem cells and electrical stimulation (ES) for nerve regeneration. This article focuses on advances in nerve transfers for lower extremity PNI and provides details on the basic science and clinical applications of newer interventions.

Keywords: Stem cells, peripheral nerve, surgery, nerve transfer, electrical stimulation, nerve repair, nerve regeneration

INTRODUCTION

Patients with traumatic injuries may experience pain and disability due to PNI. One recent study found that 1.2% of patients with lower extremity trauma experience PNI, and these patients are more likely to

experience chronic pain and require physical and occupational therapy[1]. Therefore, proper diagnosis and treatment are crucial for improving outcomes in these patients. Historically, more attention has been paid to peripheral nerve reconstruction of the upper extremity, with less attention focused on the lower extremity. The longer distances between nerves in the lower extremity make nerve transfers in the leg more challenging. The increased distance required for regeneration can also lead to worse outcomes, as the target muscle(s) may be atrophied by the time of regeneration[2]. Research into nerve regeneration and factors that improve outcomes is crucial for overcoming these obstacles.

There are various options for repair of lower extremity nerve injuries depending on the extent of nerve damage and subsequent nerve gap. Direct repair is the preferred treatment modality in cases where a tensionless repair is possible with a neglectable nerve gap[3]. However, in cases of severe nerve damage, nerve conduits are preferred for gaps less than 3 cm, and auto- or allografts are used for gaps of more than 3 cm[3]. However, the capacity for nerve regeneration and functionality can be limited after reconstruction by scar formation, hemostasis, and infection[3]. Interventions have been proposed to improve nerve regeneration, including adipose-derived stem cells (ADSCs)[4-7], and electrical stimulation[8-10]. Although these interventions have demonstrated potential for improving axonal regeneration and functional nerve recovery, their use in clinical settings remains unclear.

In cases with significant scarring preventing nerve graft surgery, nerve transfers may be viable interventions for restoring muscle function. Nerve transfers have the possibility of earlier reinnervation with restoration of function[11]. Anatomical and clinical studies have investigated new sites for nerve transfers and reported promising results in traumatic cases[12-14] and patients with acute flaccid myelitis[15,16]. The variability of lower extremity nerve injuries requires a personalized approach and understanding of each therapy's unique advantages and disadvantages. In this article, we will focus on the recent advances in nerve transfers and provide additional details regarding interventions to improve axonal regeneration.

NERVE TRANSFER

In upper extremity injuries, nerve transfers have been increasingly performed to restore motor function[11]. Nerve transfers allow the surgeon to avoid operating in the zone of injury, which may have scarring[11]. Another advantage is the potential for faster recovery, due to a nerve coaptation site closer to the target. Developments in nerve transfers for the lower extremity have lagged behind the upper extremity due to inherent anatomical challenges, such as increased distance for nerve regeneration and fewer nerve branches to serve as donor nerves following spinal cord injuries[2]. Other advantages of nerve transfer surgery in the lower extremity over nerve grafts arise because these injuries often require long nerve grafts, leading to a degeneration of the target distal motor endplate before reinnervation can occur[17]. Ambulation, as well as bowel and bladder control, are priorities for lumbosacral plexus injuries[2]. Examples of promising advances have been reported and are discussed below [Table 1].

Femoral nerve repair

Femoral nerve is the major branch of the L2-L4 lumbar plexus and innervates the hip flexor and knee extensor muscles. It also controls the sensory processing of the anteromedial thighs to the medial compartment of the legs and feet. Injuries to the femoral nerve may result in significant functional impairments depending on the anatomic location of the damaged nerve. Generally, femoral nerve injuries at the pelvis level are classified as high femoral nerve injuries. The first successful employment of nerve transfer for repair of high femoral nerve injury was reported in the study by Campbell *et al.* in 2010[18]. They transferred the ipsilateral obturator nerve to the injured femoral nerve, which was damaged due to a schwannoma[18]. The impressive restoration of functional outcomes after this nerve transfer was the

Table 1. Examples of the published articles on the use of nerve transfer for lower extremity nerve injuries

References	Study design Population characteristics Mean age ± SD, F; M ratio	Clinical outcome
Femoral nerve repair		
Campbell *et al.* (2010)[18]	• Case report • 45-year-old female with a retroperitoneal schwannoma involving lumbar plexus	• Excellent functional recovery and significant quadriceps functions at 2 years after the operation
Goubier *et al.* (2012)[20]	• Cadaveric study • Investigated the anatomical feasibility of obturator-to-femoral nerve transfer in 5 cadavers (10 thighs)	• Confirmed that obturator-to-femoral nerve transfer is anatomically possible and may have clinical implications
Tung *et al.* (2012)[19]	• Cadaveric study • Evaluated the efficacy of obturator nerve transfer to the femoral nerve in both human and cadaveric subjects	• Obturator-to-femoral nerve transfer is a safe and efficient procedure for the treatment of high femoral nerve injuries
Karagiannis *et al.* (2015)[53]	• Case report • 49-year-old man with right-sided femoral nerve palsy undergoing dual gracilis and adductor longus to quadriceps muscles	• Significant functional recovery at 3 years post-operation
Inaba *et al.* (2018)[54]	•Case report • Partial obturator nerve transfer was done for the repair of an excised femoral nerve after resection of a retroperitoneal schwannoma	• Significant quadriceps recovery with 4/5 knee extension and normal gait
Meng *et al.* (2018)[55]	• Animal study (rat) • Investigate the efficacy and feasibility of obturator nerve transfer for repair of injured femoral nerve in rat models	• A significant functional recovery and increase in quadriceps muscle mass in rat models after nerve transfer was observed
Rastrelli *et al.* (2018)[56]	• Case report • Anterior branch of the obturator nerve was transferred to the femoral nerve at thigh level in a 19-year-old female	• Obturator-to-femoral neve transfer is a feasible option when the nerve gap is considerable (≥ 6 cm)
Doi *et al.* (2019)[15]	• Case report • Contralateral obturator nerve transfer to the left femoral nerve due to acute flaccid myelitis	• At 14 months post-op, favorable functional outcome with full knee extension was achieved
Graham *et al.* (2020)[57]	• Case report • A modified obturator-to-femoral neve transfer with cable grafting for a 49-year-old woman with iatrogenic injury to the femoral nerve	• At 4 years post-op, patient recovered knee extension (4/5) and mobilization was successful
Cao *et al.* (2020)[14]	• Case report • Contralateral obturator nerve transfer to femoral nerve after extensive lumbar plexus injury in a 30-year-old male	• Contralateral obturator nerve transfer to femoral nerve is an alternative procedure when the ipsilateral obturator nerve is damaged
Chen *et al.* (2020)[21]	• Cadaveric study • Evaluate the safety and feasibility of sciatic nerve transfer to the femoral nerve in cadavers	• Suggested that the muscle branches of sciatic nerve may be a reasonable candidate for femoral nerve repair
Nicholas *et al.* (2021)[13]	• Case report • Reported two cases of extensive lumbosacral plexus injury accompanied with root avulsion which underwent contralateral obturator-to-femoral neve	• At the last follow-up, patients had 3/5 and 2/5 knee extension, representing this nerve transfer as a therapeutic option for extensive plexal injuries
Peters et el. (2021)[12]	• Retrospective case-series • Reported the functional outcome of 14 patients with femoral nerve palsy that underwent femoral nerve decompression and nerve transfer	• Post-operatively, a significant improvement in knee extension muscle power and pain compared with pre-operation (*P*-value = 0.001)
Lubelski *et al.* (2021)[16]	• Case-series • Demonstrated sciatic-to-femoral nerve transfer using a fascicle of the proximal tibial nerve as the donor for pediatric patients with acute flaccid paralysis	• Sciatic-to-femoral nerve transfer is a feasible option for repair of extensive lumbar plexus damage. However, the clinical outcome of patients are not available
Donaldson *et al.* (2022)[58]	• Case-series • Two patients with femoral nerve injuries underwent concomitant gracilis muscle transfer and obturator-to-femoral neve (adductor longus nerve branch)	• At 6 months post-op, one patient regained significant knee flexion and full knee extension with grade 4/5 power. • At 18 months post-op, patient 2 had full knee flexion and extension with grade 5/5 muscle power
Obturator nerve repair		
Spiliopoulos *et al.* (2011)[27]	• Case report • Femoral-to-obturator nerve transfer was done for a female patient with a iatrogenic obturator nerve injury	• At 1 year post-op, patient gained full limb adduction and full recovery was observed

	after excision of a gynecologic tumor	
Tibial nerve repair		
Koshima *et al.* (2003)[28]	• Case report • First description of nerve transfer for repair of tibial nerve using the deep peroneal nerve	• Significant improvement in patient's functional outcome. Both patients were able to walk at the last follow up
Yin *et al.* (2015)[29]	• Case-series • Evaluated the safety and efficacy of ipsilateral obturator-to-tibial nerve transfer in 5 consecutive patients with sacral plexus injury	• Significant symptom resolution was observed following the transfer • Obturator-to-tibial nerve transfer is a feasible option when direct nerve repair is not plausible
Moore *et al.* (2017)[17]	• Case-series and cadaveric study • Investigated the distal femoral-to-sciatic nerve transfer for proximal nerve injuries	• Efficient and safe transfer procedure for treatment of proximal tibial nerve injuries
Agarwal *et al.* (2018)[59]	• Prospective case-series • Saphenous nerve transfer to the posterior tibial nerve was carried out for 21 patients with loss of sensation at the sole	• At 6 months follow up, significant improvement in sensory perception was observed in most of sole territories
Meng *et al.* (2018)[33]	• Cadaveric study • Investigated the efficacy and safety of femoral nerve transfer to peroneal and tibial nerves for high sciatic nerve injury	• Femoral-to-sciatic nerve transfer is a feasible option for restoring muscle and sensory function for sciatic nerve and its branches
Namazi *et al.* (2019)[60]	• Cadaveric study • Evaluated the safety and feasibility of obturator to tibial nerve transfer with saphenous nerve graft	• This technique is feasible for patients with sacral nerve root avulsion injury. However, no clinical outcomes are available
Peroneal nerve repair		
Ferris *et al.* (2017)[31]	• Case-series • Partial tibial nerve transfer was carried out for 9 patients with traumatic peroneal nerve injury	• Excellent functional outcomes were observed for 7/9 patients. the study recommended nerve transfer as an alternative therapeutic option
Nath *et al.* (2017)[32]	• Retrospective case-series • Investigated the surgical outcomes of 21 patients with foot drop undergoing nerve transfer	• The results of the study showed significant improvement in functional outcome after the operation
Meng *et al.* (2018)[33]	• Cadaveric study • Investigated the efficacy and safety of femoral nerve transfer to peroneal and tibial nerves for high sciatic nerve injury	• Femoral-to-sciatic nerve transfer is a feasible option for restoring muscle and sensory function for sciatic nerve and its branches
Flores *et al.* (2013)[34]	• Retrospective case-series • Investigated the efficacy and outcome of 13 patients with foot drop undergoing tibial-to-peroneal nerve transfer	• Nerve transfer from the soleus muscle to the deep peroneal nerve is not recommended due to unfavorable patients outcomes

inspiration for future surgeons to utilize nerve transfer for femoral nerve injuries when a direct repair is not possible due to a considerable nerve gap. Nevertheless, performing a transfer for an injured femoral nerve at the pelvis can be challenging. Goubier and Tung assessed the anatomical feasibility of obturator-to-femoral nerve transfer and confirmed that this nerve transfer is anatomically possible[19,20]. Since then, a few modifications have been made to the femoral nerve transfer to maximize axonal regeneration and nerve viability.

One of the most robust data on nerve transfer for femoral nerve repair came from the study by Peters *et al.*[12]. They previously reported success in treating high femoral nerve palsy using the motor branches of the anterior obturator nerve to the gracilis, adductor longus, and adductor brevis muscles and the sartorius motor branches to improve quadriceps function[12]. Successful reinnervation to all four quadriceps muscles has been reported in cases where the zone of injury was inaccessible, such as after hip surgery[12]. In this example, femoral nerve decompression was offered in conjunction with nerve transfer surgery as an adjunct therapy for neuropathic pain[12].

In patients with multilevel lumbosacral plexus injuries with concomitant ipsilateral nerve damages, restoration of knee extension has been reported using the contralateral obturator to the femoral nerve

transfer[13,14]. This approach has also successfully restored knee extension in a pediatric patient with acute flaccid myelitis[15]. In cases of femoral nerve injury accompanied by bilateral obturator nerve damage, a cadaveric study by Chen *et al.* suggested the muscle branches of the sciatic nerve may be a reasonable candidate for femoral nerve repair[21]. Lubelski *et al.* demonstrated sciatic-to-femoral nerve transfer using a fascicle of the proximal tibial nerve as the donor for pediatric patients with acute flaccid paralysis[16]. However, the clinical implications and functional outcomes of this nerve transfer remain unclear.

Other proposed donors in cases of femoral nerve injury include the nerve to semitendinosus[21] and the S1 nerve root[22], as well as the intercostal, ilioinguinal, and iliohypogastric nerves[23]. Overall, the main indication of nerve transfer for repair of a high femoral nerve injury is reserved for patients for whom direct nerve repair or nerve graft surgery is not plausible.

Obturator nerve injury

The obturator nerve originates from the L2-L4 nerve roots and innervates the medial compartment of the thigh, which are responsible for adduction and external rotation of the thigh, as well as sensory processing of medial thigh. It enters the thigh after passing across the pelvis and through the obturator foramen. Obturator nerve injuries are rare and occur most commonly from complications during pelvic surgery. Injury to the obturator nerve results in weakness in thigh adduction and external rotation and sensory loss in the medial thigh. Given the surgical setting of these injuries, nerve repair is often performed intraoperatively with direct repair or nerve grafting[24-26]. Nerve transfers are less common interventions in obturator nerve injuries presenting postoperatively, with a conservative approach being preferred. However, one study reported full restoration of hip adduction and medial thigh sensation after nerve transfer of a branch of the femoral nerve to the obturator nerve[27].

Tibial nerve repair

The tibial nerve is a distal branch of the sciatic nerve (L4-S3 nerve roots) and is responsible for motor and sensory innervations to the posterior leg compartment, as well as foot and toe flexor muscles. Injuries to the tibial nerve may result in significant gait disturbance, impaired foot plantar flexion, and sensory losses. In cases of sciatic nerve injury, repair of the tibial nerve is given priority to ensure plantarflexion strength for walking and protective plantar sensation[17]. The first description of nerve transfer for repair of the tibial nerve was in the study by Koshima *et al.* in 2003[28]. They successfully used the deep peroneal nerve to restore sensory functions of the injured tibial nerve. Moore *et al.* described a novel approach for performing nerve transfer of the terminal branches of the femoral nerve supplying vastus medialis and vastus lateralis to the medial and lateral branches of the tibial nerve in cases of tibial and common peroneal nerve palsies after sciatic nerve injury[17]. Obturator nerve transfer to the tibial nerve to the medial head of the gastrocnemius has also been successful in restoring knee and ankle flexion[27]. One cadaver study found feasible targets for restoring tibial nerve function using transfers of the vastus medialis nerve branch to the medial gastrocnemius nerve branch[29]. There is a paucity of data on the utilization of nerve transfer for tibial nerve repair in the current literature. Nevertheless, all published articles reported significant improvements in functional outcomes. Nerve transfer should be taken into consideration as an alternative option, particularly for proximal sciatic nerve injuries.

Peroneal nerve repair

The common peroneal nerve is another major branch of the sciatic nerve, and it provides the motor and sensory processing of anterolateral compartment of legs to the dorsal aspect of feet and toes. The common peroneal nerve is at high risk of injury due to its superficial anatomical course, and it is the most common source of mononeuropathy in the lower extremity[30]. Peroneal nerve palsies arise from trauma, compression, or iatrogenic causes and are classically associated with “foot drop”, which results in gait

disturbance and can lead to falls[30]. In cases where conservative management fails to improve nerve function after 4 months, surgical treatment may be required with nerve decompressions, direct nerve repair, nerve or tendon transfers, or ankle fusion[30].

Nerve transfers can restore function for patients with peroneal nerve palsy. Ferris *et al.* demonstrated improvement in active dorsiflexion in patients with traumatic common peroneal nerve injuries who underwent partial tibial nerve transfer to the motor branches of tibialis anterior[31]. Another study reports successful outcomes in patients with foot drop who undergo superficial peroneal nerve or tibial nerve fascicles transfer to the motor branch of the tibialis anterior and the deep peroneal nerve[32] [Figure 1]. Feasible nerve transfers have been reported in cadaver studies by transferring the vastus lateralis nerve branch to the deep peroneal nerve branch[33]. While there is potential for nerve transfers to help patients, not all nerve transfers have excellent outcomes. Poor outcomes have been reported in the nerve of the soleus muscle to the deep peroneal nerve transfer[34].

These novel techniques demonstrate the innovation required to treat patients with PNI in the lower extremity. Nerve transfers have the potential to restore function in cases where other treatments, such as nerve grafting, are not feasible. To optimize outcomes in nerve transfers, the donor activation focused rehabilitation approach has been suggested in upper extremity nerve transfers[35]. Given the success of these interventions in the upper extremity, advances in the lower extremity are promising.

SURGICAL NEUROLYSIS

Neurolysis is another therapeutic option for patients with intractable pain that are not responsive to conventional treatments. Surgical neurolysis refers to the procedure of releasing the entrapped nerves from the adjacent tissues enabling them to decompress and repair. Pess *et al.* in 1987, described a case of femoral nerve compression following a total hip replacement that was successfully treated with surgical nerve decompression and neurolysis[36]. Since then, the implications of neurolysis for the treatment of lower extremity neuropathic pain have been discussed in the literature with favorable patient outcomes [Table 2]. The main role of neurolysis for lower extremity neuropathic pain is for patients with nerve entrapment. Decompressing the affected nerve from the adjacent fibrous tissues would lead to better functional recovery, symptom relief, and axonal regeneration. Surgical neurolysis is considered a safe and feasible option for nerve decompression [Figure 2]. Complications of surgical neurolysis have been reported rarely, and it mainly depends on surgical technique and the degree of nerve adhesions to the surrounding structures.

STEM CELL THERAPY FOR NERVE REGENERATION

Nerve transfers may provide a definitive surgical resolution to many cases of lower extremity PNI. Alternative therapies to promote axonal regeneration and improve nerve function may be required in cases where nerve transfers are not possible. Stem cells have been investigated as a therapy for PNI due to their potential to regenerate neurons, support glial cells, and release factors to promote nerve regeneration[4]. Schwann cells, in particular, play a vital role in the regenerative response, although there are challenges associated with harvesting autologous Schwann cells[37]. Schwann cells are procured by harvesting donor nerves and cell culturing, requiring the loss of a functional nerve[37]. For this reason, there have been significant advances in lower extremity nerve regeneration using stem cells and the results have been satisfactory.

Embryonic stem cells

Embryonic stem cells (ESC) are pluripotent cells and can be extracted from the inner embryonic blastocyte layer. They can actively differentiate into almost all cell lineages including neurons and glial cells, which

Table 2. Examples of published articles on the implications of nerve neurolysis in the lower extremities

References	Study description	Clinical outcome
Pess *et al.* (1987)[36]	• Case report • A patient underwent nerve decompression and neurolysis after femoral neuropathy following the use of pressurized cement in total hip arthroplasty	N/A
Montgomery *et al.* (2005)[61]	• Case report • Late surgical neurolysis for a female patient with sciatic nerve injury after total hip arthroplasty	• Full functional recover and pain alleviation after the procedure
Volpi *et al.* (2005)[62]	• Case report • Laparoscopic sciatic nerve neurolysis in a 37-year-old female due to nerve entrapment after endometriosis	• Significant improvement at the last follow up
Possover *et al.* (2007)[63]	• Case series • Laparoscopic neurolysis of proximal sciatic nerve and sacral plexus due to endometriosis infiltration	• Laparoscopic neurolysis is a feasible option for sciatic nerve entrapment
Ramanan *et al.* (2011)[64]	• Retrospective case-series • Evaluated 20 patients with commo peroneal injury that underwent surgical neurolysis	• Functional recovery was observed in 74 % and 68% of patients with motor and sensory dysfunction, respectively
Kyriacou *et al.* (2013)[65]	• Prospective cross-sectional • Investigated the functional outcome of 56 patients with sciatic nerve palsy after hip arthroplasty that underwent surgical neurolysis	• The mean VAS score decreased significantly after neurolysis • Surgical neurolysis is associated with improved functional outcome in patients with sciatic nerve injury
Maalla *et al.* (2013)[66]	• Retrospective case-series • Investigated the role of surgical neurolysis for patients with common peroneal nerve entrapment	• Excellent outcome in 9 (60.0%) patients after neurolysis
Aboulfetouh *et al.* (2014)[67]	• Case-series • Evaluate the safety and efficacy of neurolysis for treatment of sciatic nerve entrapment in 11 patients with sciatic nerve injury	• At 1-year follow up, 10 patients (90.9%) had significant motor and sensory improvement • Sciatic nerve neurolysis is a safe and efficient option for neuropathic pain without the risk of major complications
Andrade *et al.* (2015)[68]	• Case report • A 38-year-old female with femoral nerve involvement by endometriosis underwent laparoscopic neurolysis	• Laparoscopic neurolysis could be the first approach for treatment of femoral nerve endometrial infiltration
Ham *et al.* (2018)[69]	• Retrospective case-series • Investigated the outcome of patients with deep gluteal syndrome that underwent endoscopic sciatic nerve neurolysis	• Significant functional outcome with satisfactory pain reduction
Ilizaliturri *et al.* (2018)[70]	• Prospective case-series • Endoscopic sciatic nerve exploration and neurolysis for 15 patients with deep gluteal syndrome	• Excellent functional outcome with significant pain alleviation post-operation
Broekx *et al.* (2018)[71]	• Retrospective case-series • Evaluated the outcome of peroneal nerve neurolysis in patients with foot drop after weight loss	• External neurolysis is a safe and efficient procedure for foot drop with a success rate of 85%
Tarabay *et al.* (2019)[72]	• Case-series • 14 patients underwent surgical neurolysis due to common peroneal nerve entrapment	• 13 out of 14 patients reported significant motor functional recovery after decompression
Park *et al.* (2019)[73]	• Comparative study • Compared functional outcome of patients undergoing neurolysis after acetabular fracture *vs.* deep gluteal syndrome	• Neurolysis was associate with favorable outcomes in both groups; however, patients with deep gluteal syndrome were associated with better outcomes

accounts for their regenerative effects[38]. An animal experiment by Cui *et al.* demonstrated that after the transplantation of ESC-derived neural progenitor cells at the site of sciatic injury, the stem cells differentiated into myelin-producing cells[38]. The transplanted progenitor cells can potentially replace the injured neuron and improve functional outcomes[38]. In another animal study, genetically modified human ESC overexpressing fibroblast growth factor 2 (FGF2) was successfully employed for sciatic nerve injury, which was associated with both sensory and motor resolution[39]. Almost all experimental studies on the use of ESCs for the treatment of lower extremity nerve damage have pointed to their potential regenerative effects [Table 3]. However, a few ethical concerns are limiting the use of ESC in human subjects. The main

Table 3. Key papers regarding the implications of stem cell therapy for lower extremity nerve regeneration

References/Title	Study design	Clinical outcome
ESC		
Cui *et al.* (2008)[38]	• Animal study (rat) • Investigated rat ESC-NPCs' efficacy in repairing severe sciatic nerve injury	• Transplanted ESC can differentiate into myelin-producing cells after cell induction and have the potential to repair damaged peripheral nerve injuries
Mozafari *et al.* (2018)[39]	• Animal study (rat) • Investigating the efficacy of modified ESC with overexpressing FGF-2 for sciatic nerve injury in rat models	• Significant motor and sensory recovery were observed after modified ESC at the damaged sciatic neuron
Jones *et al.* (2018)[74]	• Animal study (rat) • Explorated the results of hESC-derived neural crest in the sciatic nerve regeneration	• *In-vivo* transplantation of hESC-derived neural crest was suggestive of significant regeneration at the site of sciatic injury
Chen *et al.* (2020)[75]	• Animal study (rat) • Described the possible role of hESC-NPCs in the regeneration of sciatic nerve	• hESC-NPCs and their microvesicles have the potential to promote sciatic nerve regeneration
iPSC		
Wang *et al.* (2011)[42]	•Animal study (rat) • Reported electrophysiological results of sciatic nerve injury following NCSC derived from iPSC and ESCs	• Combination of engineered scaffolds and multipotent stem cells has a higher therapeutic potential for nerve regeneration
Huang *et al.* (2017)[43]	• Animal study (rat) • Investigate the regenerative effects of various differential stages of human fibroblast-derived iPSCs in the function of transected sciatic nerve	• iPSC-derived NCSCs were associated with much better short and long-term sciatic nerve regeneration compared with the induced adult Schwann cells
Xia *et al.* (2019)[76]	• Animal study (rat) • Investigated the combination therapy of LIPUS with iPSC-NCSC	• A combination of LIPUS treatment with iPSC-NCSC, GDF5, and PFTBA can provide a satisfactory outcome for sciatic nerve regeneration
Lv *et al.* (2015)[77]	• Animal study (rat) • Investigating the efficacy of LIPUS with iPSC-NCSC for regeneration of transected sciatic nerve in animal models	• Results reported a higher rate of regenerated neurofilaments and vasculature with LIPUS stimulation following iPSCs-NCSC seeding
Yokoi *et al.* (2018)[78]	• Animal study (rat) • Comparing sciatic nerve regeneration in young and old-aged mice following iPSC-derived neurospheres	• Sciatic nerve regeneration was much slower in old-aged mice compared to younger ages. • Adding the iPSC-derived neurospheres to the nerve conduit was associated with better axonal regeneration
Pepper *et al.* (2017)[79]	• Animal study (rat) • Investigating whether motor neurons derived from human iPSCs have the potential to engraft into animal sciatic nerve	• Although EMG studies reported no signs of functional recovery, the motor neurons in 40.6% of rat models had successful engrafted to the denervated muscles
BMMSCs		
Dezawa *et al.* (2001)[45]	• Animal study (rat) • Efficacy of BMMSCs from rat models for regeneration of injured sciatic nerve	• Significant nerve fiber regeneration following administration of genetically engineered BMMSC to the end of transected sciatic nerve
Chen *et al.* (2006)[46]	• Animal study (rat) • Bone marrow-harvested MSCs were genetically engineered and transplanted at the nerve regeneration chamber	• The experiment resulted in an increase in regenerative nerve fibers after differentiation of BMMSCs to Schwann-like cells
Raoofi *et al.* (2021)[80]	• Animal study (rat) • BMMSCs were extracted from axotomy rat models and added to the neve conduit loaded with PCL	• Better nerve regeneration with BMMSC conditioned medium provides satisfactory results for nerve regeneration
Zheng *et al.* (2018)[81]	• Animal study (rat) • Denervated Schwann cells were co-cultured with neurons induced from BMMSCs *in vitro* • The induced neurons were added to the crushed sciatic nerves in rat models (*in vivo*)	• Co-culturing was associated with rapid denervated SC proliferation and enhancing the myelination process
Fernandes *et al.* (2018)[82]	• Animal study (rat) • Compared BMMSC *vs.* ADSC for regeneration of lesioned sciatic nerve in rat models	• Nerve regeneration was not satisfactory for both groups when using Matrigel as a conductor
Cai *et al.* (2017)[83]	• *In vitro* and *in vivo* (animal study) • Schwann-like cells were derived from human BMMSCs and used for sciatic nerve regeneration	• Bone marrow derived SC-like cells has a potential for satisfactory axonal regeneration and augmented myelination
ADSCs		

Karakol *et al.* (2022)[84]	• Animal study (rat) • Investigating the effects of epineural tubulization (ENT) with/without ADSCs for sciatic nerve transection	• Satisfactory axonal regeneration and outcome following ENT+ intratubal ADSC
Soto *et al.* (2021)[85]	• Animal study (rat) • ADSCs were magnetically recruited to the traumatic sciatic nerve for regenartion	• A safe delivery method for neuronal regeneration with satisfactory outcomes
Bucan *et al.* (2019)[86]	• Animal study (rat) • Effects of ADSC-derived exosomes on sciatic nerve remyelination	• Satisfactory axonal regeneration and outcome
Fernandes *et al.* (2018)[82]	• Animal study (rat) • Compared BMMSC *vs.* ADSC for regeneration of lesioned sciatic nerve in rat models	• Nerve regeneration was not satisfactory for both groups when using Matrigel as a conductor
Allbright *et al.* (2018)[87]	• Animal study (rat) • Investigate the role of ADSC with PCL delivery system for repair of sciatic nerve injury	• Enhanced sciatic nerve regeneration and facilitated muscle reinnervation were observed
Luca *et al.* (2017)[88]	• Animal study (rat) • Evaluated the efficacy of ADSCs with a fibrin gel delivery loaded with laminin	• Implantation with laminin was associated with satisfactory axonal regeneration

ESC-NPC: Embryonic stem cell-derived neural progenitor cell; LIPUS: low-intensity ultrasound; hESC: human embryonic stem cell; iPSC: induced pluripotent stem cell; NCSC: neural crest stem cell; EMG: electromyography; BMMSCs: bone marrow-derived stem/stromal cells; MSC: mesenchymal stem cells; PCL: polycaprolactone; SC: schwann cell; ADSC: adipose-derived stem cells.

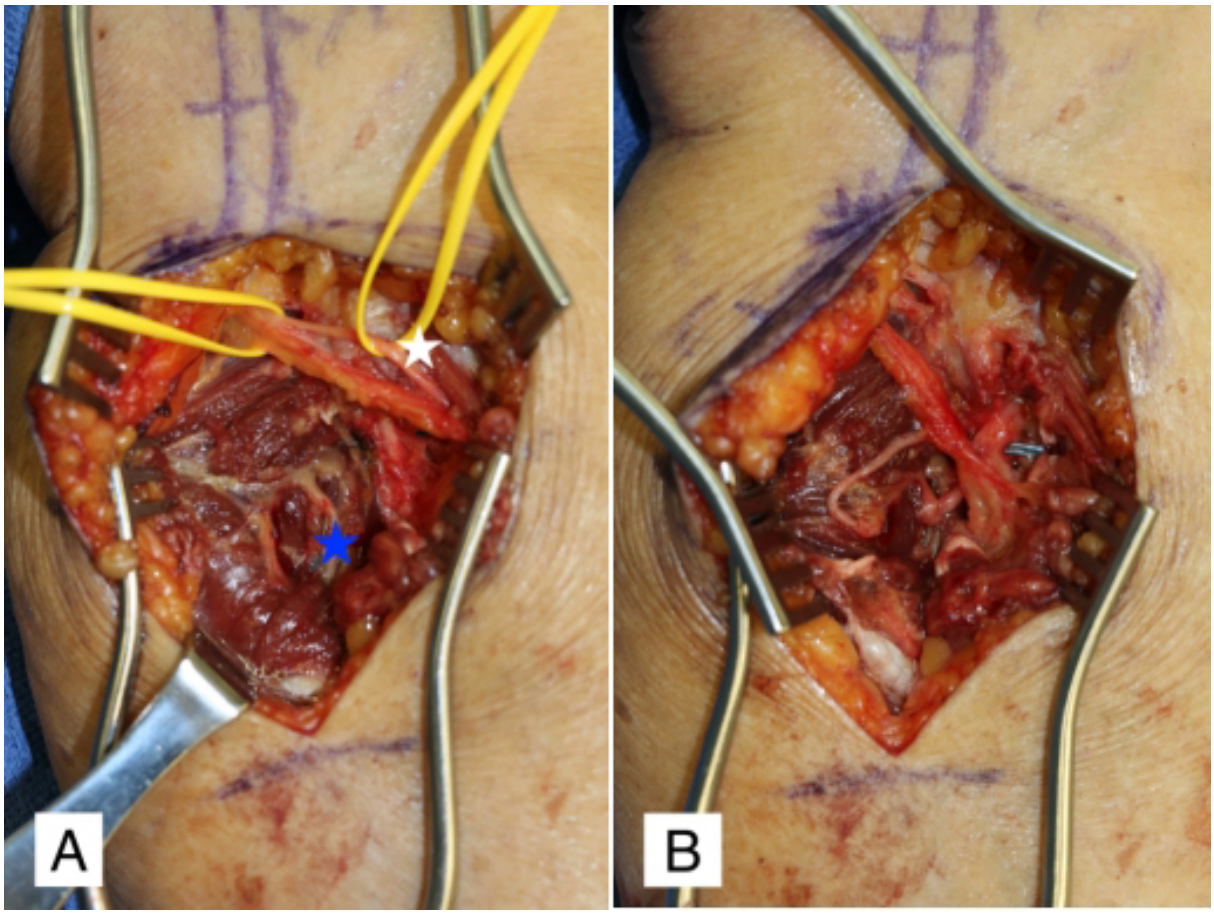

Figure 1. Nerve transfer for common peroneal nerve palsy in a 77-year-old female. A: The tibial nerve branch to lateral gastrocnemius (blue star) and the peroneal nerve branch to tibialis anterior nerve (white star) were identified. B: Nerve transfer of the tibial nerve branch to lateral gastrocnemius to the peroneal nerve branch to tibialis anterior.

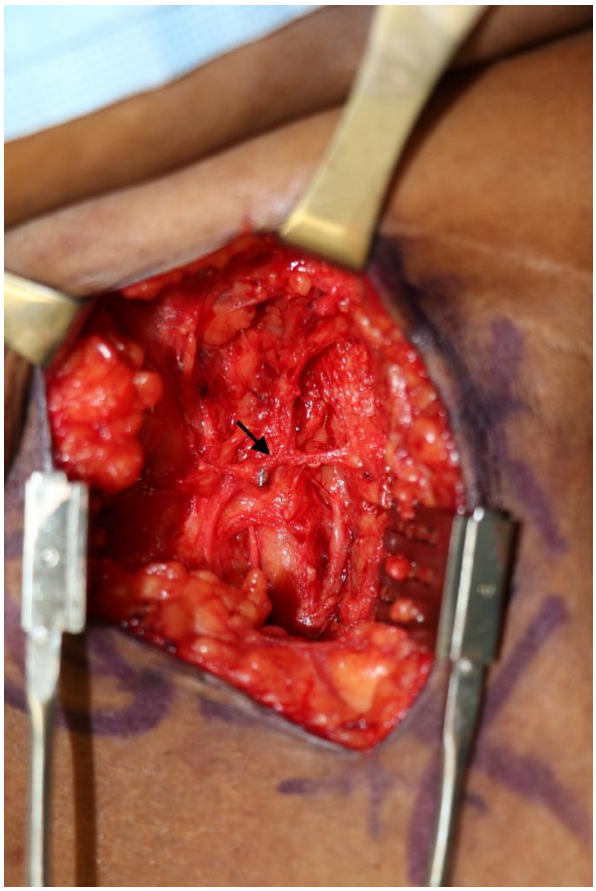

Figure 2. Femoral nerve neurolysis. A 39-year-old patient experienced traumatic neuropathic pain and a 2/5 Medical Research Council (MRC) score in knee extension. The patient had improvement in knee extension to MRC 4 function and resolution of pain following femoral nerve (black arrow) neurolysis.

controversy is the potential moral status of the embryo that prohibits ESC harvesting from the inner blastocytes cell line[40].

Induced pluripotent stem cells

To avoid these ethical concerns, Takahashi *et al.* were the first to induce pluripotent stem cells from animal (mouse) embryonic or human fibroblasts using transcription factors[41]. Their study was one of the first steps toward pluripotency control in somatic cells and providing a safe method for patient-specific stem cell generation. The first use of iPSC for lower extremity nerve regeneration was the study by Wang *et al.*, in which they used iPSCs and ESCs to derive natural crest stem cells (NCSC) for the regeneration of sciatic nerve damage in rat models[42]. They observed that NCSCs can promote nerve myelination and regeneration[42]. Huang *et al.* conducted an experiment to investigate the regenerative effects of various differential stages of human fibroblast-derived iPSCs in the function of transected sciatic nerve[43]. They observed that the iPSC-derived NCSCs were associated with much better short and long-term sciatic nerve regeneration than the induced adult Schwann cells[43]. That said, there is one major concern regarding the employment of iPSCs and their derivatives in human subjects. Compared with ESCs, iPSCs and their derivations are susceptible to oncogenic transformations due to the pluripotency induction and overexpression of oncogenic factors[44]. Although various strategies have been introduced to diminish the potential tumorigenicity, their use has been limited to animal models only. A summary of the implications of iPSC for lower extremity nerve regeneration is obtained in [Table 3].

Bone marrow-derived mesenchymal stem cell

Bone marrow-derived mesenchymal stem cells (BMMSCs) are another source of pluripotent cells that are located in the stromal bone marrow compartment. Under specific experimental conditions, they have the potential to differentiate into mesenchymal lineages, which accounts for their extensive application in cell-based therapies. The first use of BMMSCs for lower limb nerve regeneration was described by Dezawa *et al.* in 2001[45]. They observed significant nerve fiber regeneration following administration of genetically engineered BMMSC to the end of transected sciatic nerve[45]. The same observation was made by Chen *et al.* using BMMSCs from rat models for regeneration of injured sciatic nerve[46]. The experiment resulted in an increase in regenerative nerve fibers after differentiation of BMMSCs to Schwann-like cells. Regardless of their potential beneficial effects, they are limited by their harvesting difficulties, which are usually quite painful. In addition, bone marrow aspirations provide low amounts of stem cells, most of which may get lost due to unsuitable post-translational microenvironment.

Adipose-derived stem cells

Contrary to BMMSCs, adipose-derived stem cells (ADSCs) are the preferred method due to the ease of harvest in great numbers[37]. However, ADSCs are acquired after 2-3 weeks of cell culturing[5]. To address this problem, a stromal vascular fraction (SVF), which is obtained by treating subcutaneous adipose tissue with collagenase, has emerged as a potential source of ADSCs that are immediately available and do not require cell culturing [Figure 3][5].

In 2020, Mathot *et al.* demonstrated enhanced neoangiogenesis of decellularized sciatic nerve graft defects with ADSCs in rats[48]. Notably, their protocol for cell harvesting is approved for harvesting ADSCs from patients as part of a future clinical trial[48]. ADSCs have also shown potential for improving nerve regeneration in rat studies when delivered to fibrin[6] and nerve conduits[7]. Furthermore, in another study by Shimizu *et al.*, both ADSCs and SVF were shown to have excellent effects on nerve regeneration in a rat model with nerve conduits[5].

Clinical trials investigating the use of ADSCs are limited by the Food and Drug Association, which has not approved using ADSCs that have been enzymatically altered[49]. These federal regulations limit the availability of ADSCs for research, warranting further investigation into alternative sources[37]. One target source of mesenchymal stem cells is the olfactory nerve[50]. An additional intervention showing potential is the use of fat grafting as a source of ADSCs[37]. This is an evolving field of research, and more studies are needed to investigate patient outcomes[49].

ELECTRICAL STIMULATION

An additional intervention to encourage nerve regeneration after PNI is pulsatile ES, which has shown potential as an adjunct therapy by accelerating axonal regeneration and promoting recovery[10]. Keane *et al.* found that ES accelerated functional recovery when applied at the time of nerve graft surgery in rats[8]. Immunohistochemistry of the harvested nerve revealed increased axonal regeneration and macrophage accumulation[8]. Furthermore, Jo *et al.* found that ES improved nerve regeneration in a rat model and was comparable to the changes seen with systemic tacrolimus administration[9].

One challenge in the translation of ES at the time of surgery to a clinical setting is that the current protocol tested is one-hour in duration, which adds a significant time and cost burden for clinical trials[10]. Roh *et al.* found a possible solution to this problem by investigating the benefit of a 10-minute ES session in a rat model[10]. They found accelerated recovery in both the 10- and 60-minute ES groups compared to the control group, with evidence of early axon regeneration in both groups[10]. While no clinical trials have been

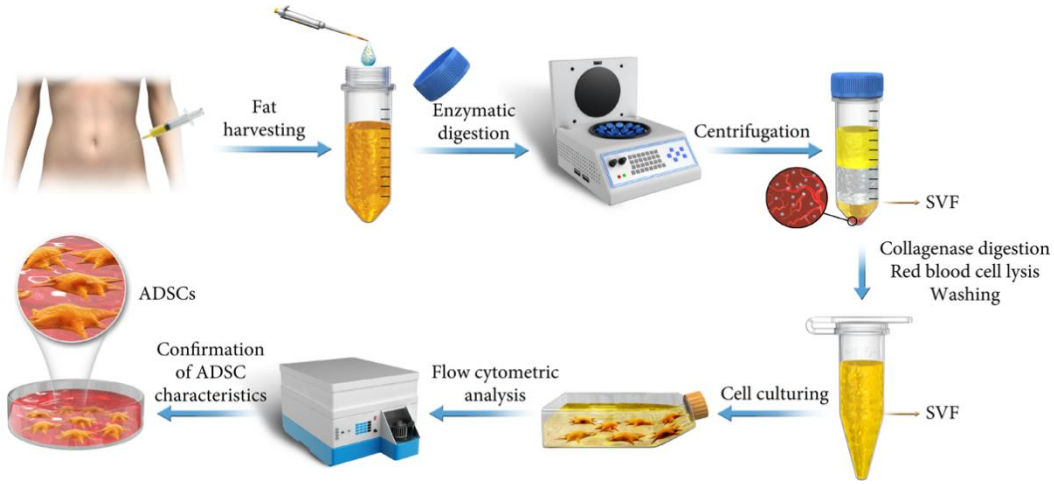

Figure 3. Subcutaneous adipose tissue can be harvested and treated with collagenase to produce SVF, which can be cultured for 2-3 weeks to produce undifferentiated ADCSs[37,47]. These cells can be differentiated into ADSCs, which can in turn promote nerve regeneration[37].

published investigating ES in PNI in the lower extremity, one recent clinical trial found improved outcomes in patients treated with adjuvant ES during surgery for severe cubital tunnel syndrome[39]. However, more clinical trials are needed to evaluate the clinical applications of electrical stimulation in the lower extremity.

ES can be provided at the time of nerve repair or as part of a long-term approach with a neuroprosthesis. For example, in a case series by Possover *et al.*, 29 patients with spinal cord injuries had long-term low-frequency ES of the pelvic somatic nerves with a neuroprosthesis implanted laparoscopically at the time of surgery[51]. While some patients were reported to have improved sensory and motor function recovery, this study was limited by its design, and further studies are needed to confirm the benefits of ES[51]. Notably, one concern with implantable neuroprosthesis is an induced foreign body reaction, which can compromise benefits by provoking an inflammatory response[52]. However, systemic dexamethasone treatment for 2 weeks in rats was found to significantly attenuate the inflammatory response, demonstrating a potential adjuvant therapy to improve the function of neuroprostheses[52].

CONCLUSION

There have been many significant advancements in peripheral nerve surgery, though advances in the lower extremity have lagged behind the upper extremity. Nerve transfers have been successfully performed in the upper extremity and translated to the restoration of function in the lower extremity. Meanwhile, new targets are being evaluated for their anatomical feasibility through cadaver studies, with case reports of successful implementation in surgery. Nerve regeneration has been researched, primarily through basic science studies, as a critical step that can be improved through ADSCs and ES.

Given the impact of lower extremity PNI on patient well-being, there must be a concerted effort to investigate the benefit of the discussed interventions through continued research. While there are challenges in translating basic science research to the clinical setting, the proposed interventions can be optimized. One key challenge in using ADSCs is finding a source of cells that is readily available and complies with federal regulation, thereby leading to investigations into fat grafting[37]. In ES, the current protocol relies on an hour-long session at the time of surgery, leading to research into a possible shortened duration as a solution[10]. Innovative solutions like these can promote continued advancement; however, clinical trials are

necessary before these interventions become standard practice.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the review: Garbuzov A, Nichols DS, Chim H

Review of literature, manuscript writing and critical revisions: Shekouhi R

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All authors declared that there are no conflicts of interest.

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Consent for publication

Not applicable.

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