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Review article about End to End sciatic Nerve Injury Repair at Different Angles of Attachment

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Abstract: Background: Sciatic nerve injuries are most commonly seen in war/combat-related injuries, with the literature describing peripheral nerve injuries associated with as many as 30% of combat-related injuries. These include penetrating mechanisms, such as blast shrapnel, gunshot wounds, or bone fragments/fractures as the secondary injury mechanism after explosions. Animal studies in rat sciatic nerve and rabbit common peroneal nerve models have demonstrated improved axon counts and gait function after end-to-end coaptation with a PTB nerve wrap. Improved gait function has also been demonstrated in a one cm rat sciatic nerve graft model. End-to-end repair is preferred for transected nerves with short gaps . However, if such a repair places the nerve or the site of repair under substantial tension, outcomes are likely to be poor and repair failure emerges as a significant concern ; so, an intervening graft or conduit is deployed.

Keywords: *Sciatic Nerve Injury, Repair, End to End Sciatic Nerve Repair*

Introduction

Sciatic nerve injuries are most commonly seen in war/combat-related injuries, with the literature describing peripheral nerve injuries associated with as many as 30% of combat-related injuries [1]. These include penetrating mechanisms, such as blast shrapnel, gunshot wounds, or bone fragments/fractures as the secondary injury mechanism after explosions [1].

In addition, due to the diameter, length, and regeneration distance of the nerve, repairs lead to significant challenges and dilemmas. Ultimately, for these reasons, many studies have illustrated poor functional outcomes and high complication rates following sciatic nerve repair in both civilian and military practices [2].

Axonal regeneration occurs exclusively in peripheral nerves. Wallerian degeneration occurs at the distal axonal stump, and growth cone formation occurs at the proximal axonal stump. In complete nerve transections, this recovery process can be hindered by neuroma formation. Incomplete regeneration requires appropriate treatment to avoid permanent muscle atrophy and functional loss [3].

Surgical repair aims to reestablish continuity between the proximal and distal nerve stumps to restore innervation of end target receptors. Sciatic nerve injuries are commonly repaired directly or reconstructed with autologous nerve grafts along with neurolysis. Direct (end-to-end) repair is exclusively performed when

the gap is short and tension-free repair is possible. This is accomplished by approximating the ends with tissue-fibrin glue or by coapting the epineurium with sutures [4].

On the other hand, nerve grafts are required when the gap is too extensive to allow tension-free repair. The sural nerve is the most common donor nerve used. Neurolysis aims to remove scar tissue between the fascicles (internal neurolysis) or from around the nerve (external neurolysis). Surgical neurolysis involves dissection and exploration of a damaged nerve with the goal of freeing the nerve from local tissue restrictions or adhesions. Additionally, multilevel segmental injuries may require a combination of techniques [5].

Since the research by Roganović et al. was published, many studies have evaluated the use of newer techniques, such as nerve transfers. Nerve transfers are used to augment motor and sensory recovery after injury. It involves using an expendable donor nerve that serves the equivalent function as another nerve in the body and affixing it to a denervated (injured) nerve in an end-to-end or end-to-side fashion. Hence, the rerouted nerve can aid motor or sensory recovery distal to the injury site [6].

A study evaluated the use of nerve transfers to provide better outcomes than those seen with alternative techniques. The transfer technique was carried out on 2 male patients with sciatic nerve injuries resulting in complete palsy. Both patients underwent a transfer of distal motor branches of the femoral nerve to the gastrocnemius nerve, along with the transfer of the saphenous nerve to the sural nerve for sensation [7].

The researchers found that both patients achieved motor recovery of MRC grade 3 and 3+ in plantar flexion by 18 months postoperatively. The patients also recovered sensation, which was signified by the Tinel sign. Interestingly, it was found that direct end-to-end repair of nerves yielded better functional outcomes than the use of a graft in nerve transfers [8].

This study shows that the femoral nerve has promising use as a nerve transfer donor with sufficient reinnervation to distal nerves. These further support the potential use of nerve transfers in sciatic nerve repairs. The outcomes of sciatic nerve repair are relatively poor and debilitating, even with lesions in continuity requiring only neurolysis. The reasons for this could be attributed to the highly traumatic nature of these injuries, which were frequently segmental, multilevel injuries involving long regeneration distances [9].

Sciatic Nerve Graft Regeneration in Male Albino Rats

Animal studies in rat sciatic nerve and rabbit common peroneal nerve models have demonstrated improved axon counts and gait function after end-to-end coaptation with a PTB nerve wrap. Improved gait function has also been demonstrated in a one cm rat sciatic nerve graft model [10].

Research strategies to improve recovery after nerve repair fall into two main categories: methods that enhance axonal regeneration and methods that decrease environmental inflammation. Methods to enhance axonal regeneration can be further broken down into: (Section 1) enhancing axonal sprouting from the distal nerve stump (growth factors; electrical stimulation of the proximal stump); (Section 2)

Enhancing Axonal Regeneration

1.1. Growth Factors

Nerve growth factors (neurotrophins) are molecules that are naturally released in the process of nerve regeneration. They are released from the nerve ending, especially following a nerve injury, and have an effect on nerve growth, differentiation, and surveillance. A number of these neurotrophic factors have been isolated and applied to the proximal nerve stump after injury to enhance axonal regeneration [11].

Nerve growth factor (NGF) is present at low concentrations in healthy nerves. Following nerve injury, NGF is upregulated in the distal nerve stump and plays an important role in the survival of sensory neurons and outgrowth of their neurites. There are numerous other growth factors that have been identified during nerve regeneration, including Glial growth factor (GGF), fibroblast growth factor (FGF), glial cell-derived neurotrophic factor (GDNF), neurotrophin 3 (NT-3), ciliary neurotrophic factor, and leupeptin [11].

NGF, GGF, GDNF, and NT-3 have been applied in nerve conduits to small animal models of nerve gap injury (1–4 cm gap), demonstrating improved histological, electrophysiological, and functional outcomes compared to conduit controls. However, one of the few studies comparing NGF-seeded conduits versus nerve autografts

demonstrated superior functional outcomes in the autograft group. Future application of growth factors in combination or via sustained release delivery systems or scaffolds could further enhance axonal regeneration, particularly for conduits in nerve gap injuries [12].

1.2. Electrical Stimulation

There have been limited reports of applying electrical fields/gradients across a repaired peripheral nerve to speed up axonal regeneration. Animal studies demonstrate that as little as one hour of direct nerve electrical stimulation immediately after repair of a transected femoral nerve in the rat promotes a dramatic increase in the kinetics of target muscle reinnervation [13].

In a clinical pilot study, one hour of electrical stimulation was applied after median nerve decompression at the wrist for 21 patients with carpal tunnel syndrome and thenar atrophy. The electrical stimulation group showed evidence of accelerated axonal regeneration and target reinnervation through motor unit number estimation and sensory and motor nerve conduction studies [14].

Optimizing Axonal Regeneration across a Coaptation

2.1. Nerve Conduits

The ideal synthetic conduit should be permeable enough to provide sufficient diffusion of oxygen and metabolites for supporting Schwann cells proliferation, but should also prevent fibroblast infiltration. Schwann cell migration into nerve conduits or acellularized allografts is insufficient beyond 2 cm and is therefore one of the major limiting factors to axonal advancement over large gaps [15].

The engineering challenges for nerve repair are to accommodate larger deficits (diameter and length), maximize the number of regenerating axons, and guide axons with target specificity. An effective nervous tissue construct may require some combination of three primary components: a scaffold, cells, and signaling factors. Scaffolds provide a temporary structure necessary for Schwann cell migration and axon outgrowth, and are eventually replaced with host cells and extracellular matrix [16].

Different growth factors can be incorporated directly (in solution), into the tube's lumen, or through a delivery system. Because the effect of growth factors is often dose-dependent and requires their release over extended periods, delivery systems are generally preferred [11].

2.2. Nonthermal Laser Amnion Wrap

Photochemical tissue bonding (PTB) creates a covalently bonded nerve wrap around a nerve coaptation, using an Nd/YAG laser, photoactive dye, and a nonimmunogenic amnion wrap. The problems of unintended thermal injury to nerve tissue from traditional laser techniques are avoided [10].

Collagen fibers in the amnion wrap are covalently bonded to collagen in the epineurium. This bond adds strength to the repair, concentrates neurotrophic and neurotropic factors inside the coaptation where they are needed, excludes inflammatory mediators from the extrinsic tissues, and contains regenerating axons, guiding them distally towards the motor/sensory target [12].

Animal studies in rat sciatic nerve and rabbit common peroneal nerve models have demonstrated improved axon counts and gait function after end-to-end coaptation with a PTB nerve wrap. Improved gait function has also been demonstrated in a one cm rat sciatic nerve graft model [17].

2.3. Thermal Laser Welding

Thermal laser achieves tissue bonding by denaturation of structural proteins, which anneal and join when cooled. Tse and Ko reported successful nerve coaptation by laser welding in 1985; however, this was followed by reports of frequent dehiscence of 12% to 41%. To prevent dehiscence, one or two stay sutures can be placed before laser welding; however, nylon stay sutures lose their tensile strength when irradiated with a CO2 laser [18].

Although CO2 laser-welded nerve adhesion has demonstrated favorable results in animal models, its clinical use can be cumbersome, and its versatility is limited. Concerns remain about the high rate of nerve dehiscence and thermal injury to axons and nerve tissue [18].

2.4. Glue Repair

Advantages of an adhesive for nerve repair include ease of use, less tissue trauma, maintenance of nerve architecture, better fascicular alignment, and less scarring compared to microsutures [18].

The ideal glue should not induce fibrosis that can lead to nerve compression and in the case of substance interposition between nerves, it should not act as a barrier to nerve regeneration. The glue should provide adequate mechanical strength to prevent gapping or rupture at the initial repair and during the postoperative period [18].

Fibrin sealants have a proven track record as a safe and effective nerve glue. The longest and greatest experience with nerve glue is in brachial plexus reconstruction. In this setting, fibrin glue has been indispensable [18].

Nerve glue allows repairs to be performed at or immediately within the bony foramen of a proximal nerve root where quality suture repair is not possible [18].

A systematic review of fibrin glue for peripheral nerve repair revealed 14 animal studies, 1 cadaver study, and 1 human study that fit the study criteria. Most found fibrin glue repair to be equal or superior to suture repair [19].

However, in clinical practice, concerns remain about the lack of adequate tensile strength for fibrin glue repair alone. A biomechanical study of rabbit sciatic nerve repair reported inferior load to failure and load to gapping with fibrin glue only relative to suture repair immediately after repair. Similar inferior load to failure results have been found in a rat sciatic nerve model immediately and 7 days after repair. Fibrin glue repair was equal in strength to suture repair after a delay of 14 and 28 days. Therefore, in clinical practice, fibrin glue is predominantly used as an adjunct to microsutures or to coapt nerves where suturing is not possible, for example, intervertebral foramen [18].

Another biocompatible glue is PEG hydrogel, which demonstrates stronger adhesion than fibrin glue without being neurotoxic. In a rat sciatic nerve model, Lin and coworkers created a 5-mm nerve defect as a model of nerve coaptation under tension and repaired the nerve with 10-0 nylon epineural sutures, fibrin glue, or PEG hydrogel [20].

PEG may be superior to fibrin glue because of its greater tensile strength and longer duration before breakdown (4 weeks). PEG is nontoxic and biocompatible, and does not induce a significant inflammatory response. What may be an additional advantage is that it may have adhesion-inhibiting properties that prevent perineural scarring. PEG hydrogel is therefore a promising candidate as a nerve glue [18].

End-to-end repair

End-to-end repair is preferred for transected nerves with short gaps. However, if such a repair places the nerve or the site of repair under substantial tension, outcomes are likely to be poor, and repair failure emerges as a significant concern. So, an intervening graft or conduit is deployed [21].

Hollow conduits are acceptable for relatively short gaps, but for modest to long gaps, autografts remain the gold-standard. Despite their utility, autografts have many disadvantages, including additional patient exposure to anesthesia, donor site morbidity, geometry mismatches between injured and donor nerves, and the presence of multiple interfaces across which axons must grow before even reaching the distal nerve [22].

On the other hand, despite the prevalence of graft-based repairs, there is increasing evidence that low to moderate tension may be beneficial to nerve regeneration. In vivo and ex vivo models suggest accelerated axonal or nerve outgrowth under tension, and direct end-to-end nerve repairs under slight tension in fact outperform tension-free graft repairs for modest nerve gaps [23].

Microsurgical end-to-end epineural suturing is the most common method of repair. In addition, repair with nerve conduits has been used, where nerve ends are placed near each other within conduits. Tissue glue can be used instead of epineural sutures to approximate the nerve ends. Nerve gaps of 3-5 cm have been studied with allograft or autograft nerve grafts [24].

However, current clinical practice does not recommend end-to-end repairs for certain transection injuries, due to the possibility of excess tension along the nerve and at the repair site. Attempting the repair can result in tissue damage and catastrophic repair failure [25, 26]. Because of this rationale, surgeons typically use a graft to repair any nerve gap larger than 3 cm in length [22].

End-to-end repairs have been successfully completed following nerve lengthening across a nerve gap, with variable outcomes. Despite these successes, nerve-lengthening strategies have not yet been translated, possibly due to the invasiveness of lengthening strategies and/or inconclusive outcomes [27].

If an end-to-end repair fails, the results are catastrophic. Because functional outcomes cannot be evaluated until weeks to months after the repair, failure may often not be detected until a very late time point. Therefore, clinical practice has tended to steer more conservatively, avoiding tension as much as possible during nerve repairs [28].

However, if failure does not occur, outcomes are better for tensioned end-to-end repairs than grafts, even at moderate strains. These findings are consistent with clinical evidence of the superiority of end-to-end repairs over grafts, especially in clinical situations that require very long grafts. Thus, there is a significant benefit to developing strategies that facilitate safe end-to-end repair of severed nerves [28].

End-to-end microsurgery is typically accepted as a successful therapeutic option for PNI with a small defect gap (<5 mm). Nevertheless, for chronic PNI with a big defect gap (>5 mm), the body's ability to regenerate itself is severely constrained, and an effective form of implant is required to bridge the nerve gap in order to stimulate axonal regrowth function and functional recovery [29].

The potential implants containing regenerative components like cells and an extracellular matrix in their microenvironment could provide favorable regeneration efficiency to nerve regeneration. Autografting, a typical treatment for peripheral nerve injury, demonstrates a high therapeutic impact in tissue engineering applications [30].

It is known that the most indicated technique for nerve recovery in cases of neurotmesis is the end-to-end neurorrhaphy. However, when simple connection is not possible due to the loss of structure and the presence of a gap, the technique of autologous grafting is used. This technique is capable of guiding axonal growth and joining the ends of the distal and proximal stumps [31].

Surgical technique

The sciatic nerve, originating from the confluence of five spinal nerve roots spanning from L4 to S3, stands as the most substantial and lengthy peripheral nerve within the human body. It serves a multifaceted role, encompassing both sensory and motor functions, contributing significantly to the functionality of the lower limb. Morphologically, the sciatic nerve exhibits a broad and flat configuration within the hip region, progressively assuming a more cylindrical shape as it descends towards the lower extremity, eventually spanning an approximate length of 2 centimeters [32, 33].

The sciatic nerve is discretely divided into three distinct segments based on the location of injury. The upper part pertains to injuries originating from the sciatic notch and extending to the region traversing the gluteus maximus muscle. Middle-part injuries involve damage to the deep-seated component of the nerve, commencing from the inferior border of the gluteus maximus and extending beneath the biceps femoris muscle. In the case of lower-part injuries, the sciatic nerve's divisions are isolated, with the tibial division injury site defined up to its entrance into the popliteal fossa, while the peroneal division injury site is delineated until it enters the bony groove [32, 33].

Regardless of the precise location of the incision-induced injury, a surgical approach that adheres to the anatomical trace, prioritizing the preservation of skin vascularity, is consistently employed. Following the meticulous dissection of muscular layers to expose the nerve, the knee is flexed and stabilized to alleviate tension. The use of automatic retractors facilitates the surgical procedure, conducted under the guidance of a microscope. Initial assessments involve the verification of the continuity of both nerve divisions, with probing

conducted using a nerve probe instrument. In cases of concomitant vascular injuries, vascular surgeons perform the necessary vascular repairs [34].

For primary nerve anastomosis, the nerve endings intended for reconnection are meticulously approximated, ensuring a precise end-to-end alignment of nerve fibers. Thick sutures, typically 2.0 silk suture material (26 mm round; Dogsan, Turkey), are employed to epineurally approach either the tibial or peroneal branch at a 120-degree angle from the posterior aspect. This choice of suture material is made to mitigate any potential dissection of the epineural tissue by nylon sutures. Recognizable nerve fibers are subsequently anastomosed in an end-to-end fashion through the placement of two stitches each, employing 9/0 nylon suture material (5.0 mm round; Dogsan, Turkey) [34].

It is worth noting that the primary method employed for anastomosis is through epidural sutures. The remaining 240-degree section of the nerve, and the gaps between the thick sutures in the remaining 120-degree section are meticulously sutured using 4.0 silk material (13 mm round; Dogsan, Turkey). Following the closure of anatomical layers, the knee is immobilized at an approximate 90-degree angle without extension, effectively preventing undue tension on the sutures, a crucial factor in preventing anastomotic failure [34].

End-to-End Technique

A 2-cm portion of rat sciatic nerve that was transected and then repaired back in its position. (A) Intraoperative image. (B) Schematic diagram showing the sciatic nerve (orange) and the graft (yellow). (C) Superimposed schematic on the intraoperative image [35].

Although traditional nerve repair has been improved since the introduction of the surgical microscope, and somewhat better results of nerve repair have been obtained, functional results of standard end-to-end nerve repair at a 90-degree angle are still unsatisfactory [34].

Many factors affect the functional results of nerve repair, including slow growth and an inadequate number of regenerated nerve fibers. The nerve repair site is an important bridge. An oblique nerve repair at a 30-degree angle [36, 37] was performed, increasing the contacted repair surface area, which may result in an increase in the number of regenerative fibers and better muscle recovery [36, 37].

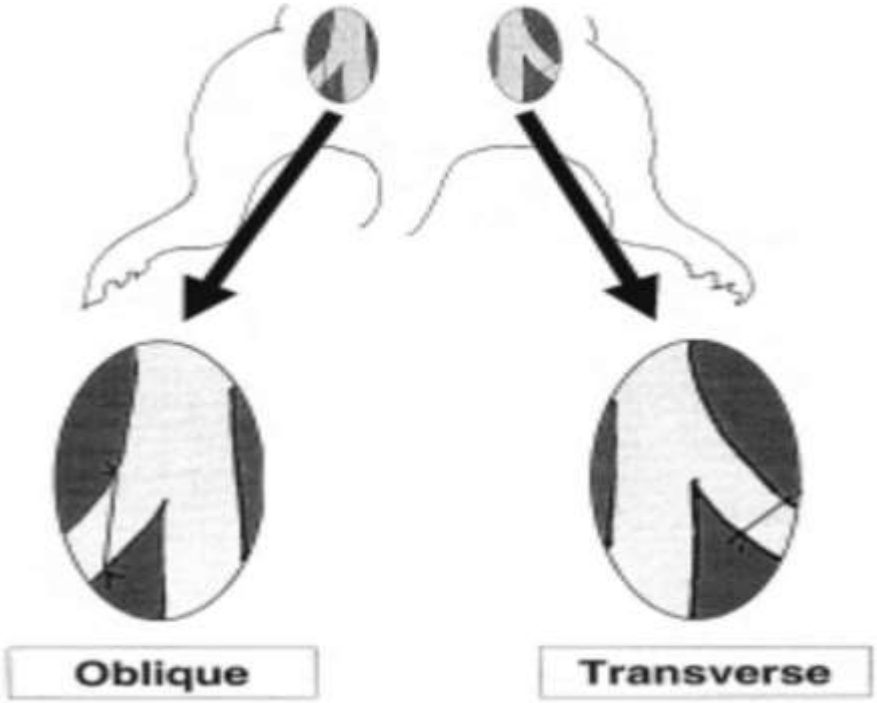

Figure 1 Two types of neurorrhaphy were performed in each rat: on the right side, standard end-to-end repair at a 90-degree angle of attachment; on the left side, oblique repair at a 30-degree angle of attachment [36].

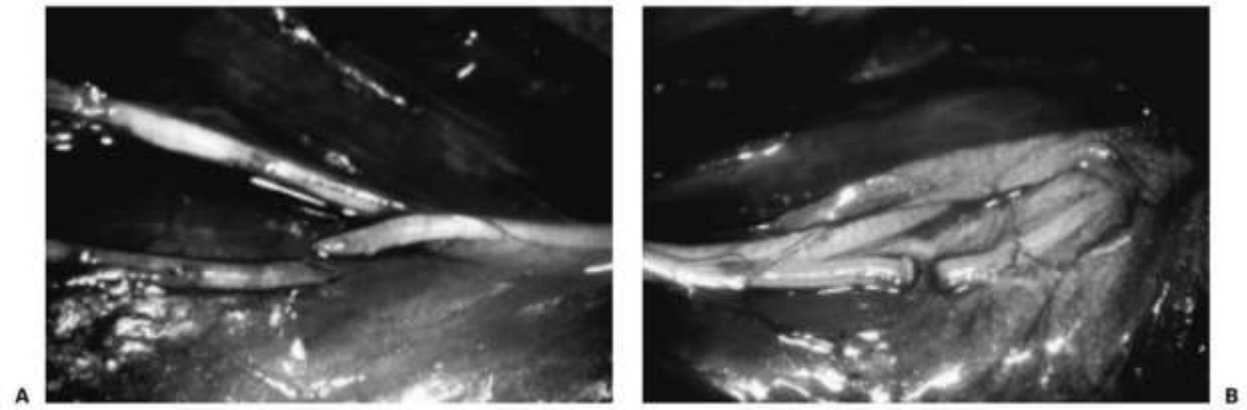

Figure 2 Illustration of surgical procedures. A, On the oblique side, the peroneal nerve was cut at a 30-degree angle; the distal angle tip of the proximal stump was 3 mm below the point of bifurcation of the sciatic nerve into the peroneal nerve and tibial nerve trunk. B, On the standard transverse side, the peroneal nerve was cut at a 90-degree angle [36].

In a study conducted by Murovic JA, favorable outcomes for tibial division anastomoses were reported at 79% at the hip level and 90% at the thigh level. Similarly, success rates for peroneal division anastomoses in Murovic's study stood at 55% at the hip level and 61% at the thigh and knee levels [38].

Further corroborating this trend, Roganovic Z reported recovery rates of 11%, 31%, and 57% for proximal-to-distal sciatic repairs resulting from gunshot wounds [39].

Nerve Regeneration between End-to-End Vs End-to-Side

In 2003, Hayashi et al. conducted one of the first studies to assess collateral sprouting that occurs following end-to-side neurorrhaphy. Using a sample size of 15 rats divided into 3 groups, the sciatic nerve was transplanted between the left and right median nerves, either end-to-end or end-to-side in three different groups. Histological analysis after 60 days concluded that nerves regenerate by collateral sprouting from the donor nerves following end-to-side neurorrhaphy [40].

In a histological study conducted by De Sá et al., using peroneal and sciatic nerves in rats (sample size of 28 rats divided into 4 groups), they concluded that end-to-side repair is not as efficient as the conventional end-to-end nerve repair. Histological analysis done after 56 days, which was retrieved 10mm distal to repair. According to these results, a quite satisfactory morphologic regeneration occurred 8 weeks after an end-to-side nerve repair [41].

Along with De Sá et al.'s study, Kanit Sananpanich et al. emphasized the same superiority of end-to-end over end-to-side in 24 rats, but after 3 months [42].

Bontioti et al. also showed superiority of end-to-end neurorrhaphy over end-to-side neurorrhaphy in a sample size of 34 rats [43].

Lundborg et al. using similar histological techniques to our study also emphasized collateral sprouting following end-to-side neurorrhaphy [44].

To the aforementioned experimental studies, end-to-side was not done extensively in humans until 1988, in which year Ulrich Mennen emphasized good clinical results in 22 patients suffering from a variety of nerve injuries, all treated with end-to-side neurorrhaphy [45:50].

References

1. Laurent Mathieu, Georges Pfister, James Charles Murison, Christophe Oberlin, & Zoubir Belkheyar. (2019). Missile Injury of the Sciatic Nerve: Observational Study Supporting Early Exploration and Direct Suture With Flexed Knee. Military Medicine, 184(11–12), e939–e944. https://doi.org/10.1093/MILMED/USZ087
2. Tufan, A. (2023a). Late Results of Early End-to-End Repair in Sciatic Nerve Injuries. Cureus, 15(10). https://doi.org/10.7759/CUREUS.47101
3. Oliveira, K. M. C., Pindur, L., Han, Z., Bhavsar, M. B., Barker, J. H., & Leppik, L. (2018). Time course of traumatic neuroma development. PloS One, 13(7). https://doi.org/10.1371/JOURNAL.PONE.0200548
4. Howarth, H. M., Kadoor, A., Salem, R., Nicolds, B., Adachi, S., Kanaris, A., Lovering, R. M., Brown, J. M., & Shah, S. B. (2019a). Nerve lengthening and subsequent end-to-end repair yield more favourable outcomes compared with autograft repair of rat sciatic nerve defects. Journal of Tissue Engineering and Regenerative Medicine, 13(12), 2266–2278. https://doi.org/10.1002/TERM.2980
5. Li, R., Liu, Z., Pan, Y., Chen, L., Zhang, Z., & Lu, L. (2014). Peripheral nerve injuries treatment: a systematic review. Cell Biochemistry and Biophysics, 68(3), 449–454. https://doi.org/10.1007/S12013-013-9742-1
6. Roganovic, Z. (2005). Missile-caused complete lesions of the peroneal nerve and peroneal division of the sciatic nerve: results of 157 repairs. Neurosurgery, 57(6), 1201–1211. https://doi.org/10.1227/01.NEU.0000186034.58798.BF
7. Grinsell, D., & Keating, C. P. (2014a). Peripheral Nerve Reconstruction after Injury: A Review of Clinical and Experimental Therapies. BioMed Research International, 2014. https://doi.org/10.1155/2014/698256
8. Safa, B., Shores, J. T., Ingari, J. V., Weber, R. V., Cho, M., Zoldos, J., Niacaras, T. R., Nesti, L. J., Thayer, W. P., & Buncke, G. M. (2019). Recovery of Motor Function after Mixed and Motor Nerve Repair with Processed Nerve Allograft. Plastic and Reconstructive Surgery Global Open, 7(3). https://doi.org/10.1097/GOX.0000000000002163
9. Wilson, T. J. (2019). Novel Uses of Nerve Transfers. Neurotherapeutics, 16(1), 26. https://doi.org/10.1007/S13311-018-0664-X
10. Grinsell, D., & Keating, C. P. (2014b). Peripheral Nerve Reconstruction after Injury: A Review of Clinical and Experimental Therapies. BioMed Research International, 2014. https://doi.org/10.1155/2014/698256
11. Konofaos, P., & Ver Halen, J. P. (2013). Nerve repair by means of tubulization: Past, present, future. Journal of Reconstructive Microsurgery, 29(3), 149–163. https://doi.org/10.1055/S-0032-1333316/ID/JR120071-28/BIB
12. Abu Rafee, M. (2017). Recent approaches for augmenting peripheral nerve regeneration: mini-review. MOJ Surgery, Volume 4(Issue 1). https://doi.org/10.15406/MOJS.2017.04.00061
13. Khuong, H. T., & Midha, R. (2013). Advances in nerve repair topical collection on nerve and muscle. Current Neurology and Neuroscience Reports, 13(1), 1–8. https://doi.org/10.1007/S11910-012-0322-3/METRICS
14. Gordon, T., Amirjani, N., Edwards, D. C., & Chan, K. M. (2010). Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Experimental Neurology, 223(1), 192–202. https://doi.org/10.1016/J.EXPNEUROL.2009.09.025
15. Pfister, B. J., Gordon, T., Loverde, J. R., Kochar, A. S., Mackinnon, S. E., & Kacy Cullen, D. (2011). Biomedical Engineering Strategies for Peripheral Nerve Repair: Surgical Applications, State of the Art, and Future Challenges. Critical Reviews™ in Biomedical Engineering, 39(2), 81–124. https://doi.org/10.1615/CRITREVBIOMEDENG.V39.I2.20
16. Gong, B., Zhang, X., Zahrani, A. Al, Gao, W., Ma, G., Zhang, L., & Xue, J. (2022). Neural tissue engineering: From bioactive scaffolds and in situ monitoring to regeneration. Exploration, 2(3). https://doi.org/10.1002/EXP.20210035
17. O'Neill, A. C., Randolph, M. A., Bujold, K. E., Kochevar, I. E., Redmond, R. W., & Winograd, J. M. (2009). Photochemical Sealing Improves Outcome Following Peripheral Neurorrhaphy. Journal of Surgical Research, 151(1), 33–39. https://doi.org/10.1016/J.JSS.2008.01.025
18. Tse, R., & Ko, J. H. (2012). Nerve Glue for Upper Extremity Reconstruction. Hand Clinics, 28(4), 529–540. https://doi.org/10.1016/j.hcl.2012.08.006
19. Sameem, M., Wood, T. J., & Bain, J. R. (2011). A systematic review on the use of fibrin glue for peripheral nerve repair. Plastic and Reconstructive Surgery, 127(6), 2381–2390. https://doi.org/10.1097/PRS.0B013E3182131CF5
20. Lin, K. L., Yang, D. Y., Chu, I. M., Cheng, F. C., Chen, C. J., Ho, S. P., & Pan, H. C. (2010). DuraSeal as a Ligature in the Anastomosis of Rat Sciatic Nerve Gap Injury. Journal of Surgical Research, 161(1), 101–110. https://doi.org/10.1016/J.JSS.2008.10.020
21. Bhatia, A., Doshi, P., Koul, A., Shah, V., Brown, J. M., & Salama, M. (2017). Contralateral C-7 transfer: is direct repair really superior to grafting? Neurosurgical Focus, 43(1), E3. https://doi.org/10.3171/2017.4.FOCUS1794

22. Grinsell, D., & Keating, C. P. (2014d). Peripheral Nerve Reconstruction after Injury: A Review of Clinical and Experimental Therapies. BioMed Research International, 2014. https://doi.org/10.1155/2014/698256
23. Simpson, A. H., Gillingwater, T. H., Anderson, H., Cottrell, D., Sherman, D. L., Ribchester, R. R., & Brophy, P. J. (2013). Effect of Limb Lengthening on Internodal Length and Conduction Velocity of Peripheral Nerve. Journal of Neuroscience, 33(10), 4536–4539. https://doi.org/10.1523/JNEUROSCI.4176-12.2013
24. Li, A., Pereira, C., Hill, E. E., Vukcevich, O., & Wang, A. (2022). In Vitro, In Vivo and Ex Vivo Models for Peripheral Nerve Injury and Regeneration. Current Neuropharmacology, 20(2), 344. https://doi.org/10.2174/1570159X19666210407155543
25. Maeda, M., Hori, Y., Sasaki, K., & Maruo, T. (1999). Nerve repair by means of nerve lengthening. Journal of Hand Surgery, 24(3), 546–553. https://doi.org/10.1053/JHSU.1999.7198
26. Sunderland, S., (2004) Nerves and Nerve Injuries, 3rd Ed., Edinburgh: Churchill Livingstone.
27. Abdelhamid, M., Yousef, A., Dionigi, P., Marconi, S., Calligaro, A., Cornaglia, A. I., Alfonsi, E., & Auricchio, F. (2015). Successful Reconstruction of Nerve Defects Using Distraction Neurogenesis with a New Experimental Device. Basic and Clinical Neuroscience, 6(4), 253. /pmc/articles/PMC4668872/
28. Howarth, H. M., Kadoor, A., Salem, R., Nicolds, B., Adachi, S., Kanaris, A., Lovering, R. M., Brown, J. M., & Shah, S. B. (2019b). Nerve lengthening and subsequent end-to-end repair yield more favourable outcomes compared with autograft repair of rat sciatic nerve defects. Journal of Tissue Engineering and Regenerative Medicine, 13(12), 2266–2278. https://doi.org/10.1002/TERM.2980
29. Georgiou, M., Golding, J. P., Loughlin, A. J., Kingham, P. J., & Phillips, J. B. (2015). Engineered neural tissue with aligned, differentiated adipose-derived stem cells promotes peripheral nerve regeneration across a critical sized defect in rat sciatic nerve. Biomaterials, 37, 242–251. https://doi.org/10.1016/J.BIOMATERIALS.2014.10.009
30. Samadian, H., Maleki, H., Fathollahi, A., Salehi, M., Gholizadeh, S., Derakhshankhah, H., Allahyari, Z., & Jaymand, M. (2020). Naturally occurring biological macromolecules-based hydrogels: Potential biomaterials for peripheral nerve regeneration. International Journal of Biological Macromolecules, 154, 795–817. https://doi.org/10.1016/J.IJBIOMAC.2020.03.155
31. Hussain, G., Wang, J., Rasul, A., Anwar, H., Qasim, M., Zafar, S., Aziz, N., Razzaq, A., Hussain, R., de Aguilar, J. L. G., & Sun, T. (2020c). Current Status of Therapeutic Approaches against Peripheral Nerve Injuries: A Detailed Story from Injury to Recovery. International Journal of Biological Sciences, 16(1), 116. https://doi.org/10.7150/IJBS.35653
32. Giuffre, B. A., Black, A. C., & Jeanmonod, R. (2023a). Anatomy, Sciatic Nerve. StatPearls.
33. Giuffre, B. A., Black, A. C., & Jeanmonod, R. (2023c). Anatomy, Sciatic Nerve. StatPearls.
34. Tufan, A. (2023b). Late Results of Early End-to-End Repair in Sciatic Nerve Injuries. Cureus, 15(10). https://doi.org/10.7759/CUREUS.47101
35. Bhandari, L., Fleissig, Y., Hoey, R., Beare, J. E., Yarberry, C., Yoshida, S., & Tsai, T. (2020). Comparison of End-to-End Technique, Helicoid Technique, and Modified Helicoid Weave Repair Technique in a Rat Sciatic Nerve Model: A Pilot Study. Cureus, 12(7). https://doi.org/10.7759/CUREUS.9196
36. Yan, Y. H., Yan, J. G., Sanger, J. R., Zhang, L. L., Riley, D. A., & Matloub, H. S. (2002). Nerve repair at different angles of attachment: experiment in rats. Journal of Reconstructive Microsurgery, 18(8), 703–708. https://doi.org/10.1055/S-2002-36503
37. M.F, G., M, M., S, H., & Khan, W. S. (2014). Suppl 1: Peripheral Nerve Injury: Principles for Repair and Regeneration. The Open Orthopaedics Journal, 8(1), 199. https://doi.org/10.2174/1874325001408010199
38. Murovic, J. A. (2009). Lower-extremity peripheral nerve injuries: a Louisiana State University Health Sciences Center literature review with comparison of the operative outcomes of 806 Louisiana State University Health Sciences Center sciatic, common peroneal, and tibial nerve lesions. Neurosurgery, 65(4 Suppl). https://doi.org/10.1227/01.NEU.0000339123.74649.BE
39. Roganovic, Z. (2005). Missile-caused complete lesions of the peroneal nerve and peroneal division of the sciatic nerve: results of 157 repairs. Neurosurgery, 57(6), 1201–1211. https://doi.org/10.1227/01.NEU.0000186034.58798.BF
40. Hayashi, A., Yanai, A., Komuro, Y., Nishida, M., Inoue, M., & Seki, T. (2004). Collateral sprouting occurs following end-to-side neurorrhaphy. Plastic and Reconstructive Surgery, 114(1), 129–137. https://doi.org/10.1097/01.PRS.0000129075.96217.92
41. De Sá, J. M. R., Mazzer, N., Barbieri, C. H., & Barreira, A. A. (2004). The end-to-side peripheral nerve repair: Functional and morphometric study using the peroneal nerve of rats. Journal of Neuroscience Methods, 136(1), 45–53. https://doi.org/10.1016/J.JNEUMETH.2003.12.018
42. Sanapanich, K., Morrison, W. A., & Messina, A. (2002). Physiologic and morphologic aspects of nerve regeneration after end-to-end or end-to-side coaptation in a rat model of brachial plexus injury. The Journal of Hand Surgery, 27(1), 133–142. https://doi.org/10.1053/JHSU.2002.30370
43. Bontioti, E., Kanje, M., Lundborg, G., & Dahlin, L. B. (2005). End-to-side nerve repair in the upper extremity of rat. Journal of the Peripheral Nervous System, 10(1), 58–68. https://doi.org/10.1111/J.1085-9489.2005.10109.X

44. Lundborg, G., Zhao, Q., Kanje, M., Danielsen, N., & Kerns, J. M. (1994). Can Sensory and Motor Collateral Sprouting be Induced from Intact Peripheral Nerve by End-to-Side Anastomosis? Http://Dx.Doi.Org/10.1016/0266-7681(94)90069-8, 19(3), 277–282. https://doi.org/10.1016/0266-7681(94)90069-8
45. Mennen, U. (2011). END-TO-SIDE NERVE SUTURE IN THE HUMAN PATIENT. Https://Doi.Org/10.1142/S0218810498000040, 03(01), 7–15. https://doi.org/10.1142/S0218810498000040
46. Mohammad-Reda A. Early post-operative results after repair of traumatic brachial plexus palsy. Turk Neurosurg. 2013;23(1):1-9. doi:10.5137/1019-5149.JTN.5654-11.3
47. Abdel-Aal, M., Ahmad, M., Ashour, H., Hemid, A. (2020). Posterior Approach to Neurotize Suprascapular Nerve by Spinal Accessory Nerve. The Egyptian Journal of Hospital Medicine, 81(4), 1804-1809. doi: 10.21608/ejhm.2020.120448
48. El-Saadi, M., Awwad, Y., Ahmad, M., Abd El Atty, N. (2022). Early Results after Repair of Cut Wrist Structures at Zone Five Volar Aspect of the Hand. The Egyptian Journal of Hospital Medicine, 87(1), 1801-1805. doi: 10.21608/ejhm.2022.230272
49. M.Tohamy, A., R.Ahmad, M., I.Elhabbaa, G., H.Abdel-Aal, M., A.Salem, A. (2022). Values of Nerve Transfer in Upper Limb Nerve Injury. Benha Journal of Applied Sciences, 7(8), 1-9. doi: 10.21608/bjas.2022.269853
50. Ahmad, M. (2018). Safety of the Prevertebral Approach for Cross C7 Transfer in Traumatic Brachial Plexus Palsy. The Egyptian Journal of Plastic and Reconstructive Surgery, 42(1), 67-74. doi: 10.21608/ejprs.2018.215066