

Systematic Review of Nerve Adhesion Barriers for Peripheral Nerve Regeneration and Functional Recovery

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Background: Peripheral nerve injury (PNI) is characterized by poor functional outcomes, insufficient nerve regeneration, and deterioration of sensory and motor function. Factors such as nerve tissue loss and extended denervation of proximal nerves impede regeneration. Therapeutic interventions include microsurgical techniques and nerve-guide conduits. However, nerve adhesion, which restricts nerve mobility, also contributes to inadequate healing. Surgical modifications and chemical agents are used to mitigate adhesion.

Methods: We searched across four databases, PubMed, Cochrane Database of Systematic Reviews, EMBASE, and Medline, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study quality and risk of bias were assessed using the systematic review center for laboratory animal experimentation (SYRCLE)'s and Cochrane RoB-2 tools.

Results: Out of 549 studies, 5 studies met our inclusion criteria, consisting of four animal studies and one randomized controlled trial involving human participants. Different nerve adhesion materials were evaluated in the studies included. Histological evaluation of nerve regeneration generally shows more advanced regenerative hallmarks in the intervention group. Additionally, in terms of motor and sensory function, improvements were seen in the majority of parameters observed in all studies included.

Conclusion: This systematic review indicates that nerve adhesion barriers show promising outcomes in promoting nerve regeneration and functional recovery by reducing adhesion and enhancing structural alignment in peripheral nerve injuries. Applicability of such barriers in humans may still be debatable as findings are limited by the small number of included studies and predominance of animal data. Further long-term trials may warrant its' clinical efficacy.

Keywords: peripheral nerve injury, nerve adhesion barrier, nerve regeneration

Introduction

PNI are a significant clinical challenge, affecting 2.8%-5% of trauma patients globally. PNI is associated with negative functional outcomes, insufficient nerve regeneration, and deterioration of sensory and motor function. The economic and social impacts of PNI are substantial, as in the United States, the annual cost of treating nerve injuries is estimated to exceed \$150 billion, accounting for surgical procedures, rehabilitation, and indirect costs such as lost productivity and long-term disability. It is characterized by inadequate recovery, muscle atrophy, chronic pain, and weakness. Various factors impede nerve regeneration after peripheral nerve damage, such as substantial nerve tissue loss and extended denervation of the proximal nerves, which elevates the risk of irreversible atrophy in innervated organs. Therapeutic interventions for peripheral nerve injury mostly consist of microsurgical techniques, such as direct repair, tension-free end-to-end suturing, and the optimal method of utilizing autologous nerve grafts for larger gaps. However, these methods are not without limitations; they often require extensive recovery times and may not restore full functionality, particularly in cases of severe injury. Recent progress in facilitating axonal regeneration has involved the creation of nerve guide

conduits, primarily focusing on the incorporation of Schwann cells or mesenchymal stem cells into synthetic permeable neural conduits.^{1,2}

Another issue observed in PNI is the regeneration and healing of injuries. Peripheral nerve regeneration is a complex process that involves several stages, including Wallerian degeneration, axonal regrowth, and remyelination. Following injury, Schwann cells play a pivotal role in facilitating regeneration by promoting axonal growth and remyelination through the secretion of growth factors and the formation of a supportive extracellular matrix.³ Effective regeneration after peripheral nerve injury depends on the presence of an appropriate milieu for regrowth. Nerve adhesion following surgery has been proven to be an issue that needs to be addressed. Nerve adhesion occurs due to excessive fibroblast activity and extracellular matrix deposition, particularly collagen, leading to scar tissue that tethers the nerve to surrounding structures. This contributes to restriction in nerve mobility, impairs vascular supply, and creates mechanical stress during movement, resulting in ischemia, chronic pain, and delayed axonal regeneration. Several emerging measures, including the use of bioengineered nerve scaffolds, neurotrophic factor delivery systems, and advanced biomaterials designed to mimic the extracellular matrix have been employed to mitigate nerve adhesion.³ Translational challenges, however, remain a significant hurdle, including the difficulty of replicating experimental successes in clinical practice, variability in patient outcomes, and long-term sustainability of these interventions.⁴

Nevertheless, there remains a lack of comprehensive research regarding the efficacy of nerve adhesion barriers in terms of functional outcomes and rehabilitation. Thus, there is a need for more dependable and effective treatments that yield improved results in individuals with peripheral nerve injuries. A systematic review would address this knowledge gap by synthesizing existing evidence and offering clinicians a clear understanding of the relative efficacy of available modalities in managing peripheral nerve injury, thereby enhancing decision-making for both clinicians and patients in clinical contexts.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Literature related to the efficacy of the nerve adhesion barrier in patients diagnosed with peripheral nerve injury or nerve adhesion was systematically searched across four databases: PubMed, Cochrane Database of Systematic Reviews, EMBASE, and MEDLINE. The general search terms used include: “peripheral nerve injury” OR “nerve adhesion” OR “nerve injury”, “nerve adhesion barrier” OR “anti-adhesion” OR “nerve barrier” OR “anti-adhesion barrier”. The search was performed on November 8th, 2024. Table 1 lists the detailed keywords used for each database. Although the language was limited to English, there were no limitations to the publishing period. Considering the author’s proficiency in English, a decision was made to present this manuscript in English to ensure

Table 1 Keywords Used for Each Database

Database	Searching Strategy
PubMed	(“Peripheral Nerve Injury” OR “Nerve Adhesion” OR “Nerve Injury”) AND (“Nerve Adhesion Barrier” OR “Anti-Adhesion” OR “Nerve Barrier” OR “Anti-Adhesion Barrier”)
Ovid.MEDLINE	1. Peripheral Nerve Injuries/ 2. Peripheral Nerve Injuries/ or Nerve Injury.mp. 3. Hyaluronic Acid/ or Hydrogels/ or Tissue Adhesions/ or Biocompatible Materials/ or Adhesion barrier.mp. or Cellulose, Oxidized/ 4. Nerve adhesion barrier.mp. 5. 1 OR 2 6. 3 OR 4 7. 5 AND 6

(Continued)

Table 1 (Continued).

Database	Searching Strategy
Ovid.EMBASE	1. Nerve regeneration/ or Peripheral Nerve Injury.mp. or peripheral nerve/ or nerve injury/ or peripheral nerve injury 2. Tissue adhesion/ or Nerve Adhesion Barrier.mp. 3. Adhesion barrier/ 4. 2 or 3 5. 1 and 4
Cochrane Library	1. MeSH descriptor: [Peripheral Nerves] explode all trees 2. MeSH descriptor: [Peripheral Nerve Injuries] explode all trees 3. Adhesion Barrier 4. #1 OR #2 5. #3 AND #4

accurate and effective communication of the content. This choice allows for a comprehensive understanding and coherent presentation of the research findings. After duplicates were removed, the titles and abstracts were screened. Potential literature that underwent a full-text review of suitable papers was included in the data synthesis. The search and screening were performed independently by three investigators with reasons for exclusion, as stated in the PRISMA flowchart (Figure 1).

Study Eligibility Criteria

The inclusion criteria for studies to be included in the analysis were as follows: 1) patients with peripheral nerve injury or animal studies modified to be present with peripheral nerve injury; 2) treated with a nerve adhesion barrier; 3) compared with placebo; and 4) reported the efficacy of treatment measured in terms of nerve regeneration rate, motor function, and sensory function. The exclusion criteria were as follows: 1) literature review, cross-sectional studies, or case reports, 2) not using English, and 3) no quantitative results. The included studies were Randomized Controlled Trials (RCT), cohort studies, and animal studies.

Data Extraction

The data extracted from each of the five included studies covered essential study characteristics and outcomes to ensure a comprehensive review. The following information was collected: 1) author and year of publication, 2) Study Design, 3) the country where the study was conducted, and 4) inclusion criteria, especially for human RCT. For animal studies, the sample size and grouping details were recorded; 5) the mean age of participants specified for RCT, while animal studies described species and strain details; 6) follow-up duration; 7) primary outcomes assessed across studies, including structural and functional parameters, such as nerve conduction velocity, myelin thickness, axon regeneration, perineural adhesion scores, and sensory recovery; and 8) summary outcomes of each study highlighting nerve regeneration rate parameters (ie, histological evaluation, nerve fiber number, myelinated nerve fiber diameter, myelin sheath thickness, myelinated axons, and width of nerve fibers) and motoric/sensoric function parameters (ie, motor nerve conduction velocity, muscle wet weight, mean ankle angles, and sensory evaluation). To ensure accuracy, three authors independently extracted data, thereby reducing the risk of errors or bias in the review process.

Quality Assessment and Data Synthesis

Quality assessment of the included studies was performed using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE)'s RoB tools to assess the risk of bias in animal studies, whereas Cochrane's RoB-2 was used to assess the risk of bias in human studies. The extracted data are summarized in tables, and narrative synthesis was conducted to describe the results. Owing to the heterogeneity of the study designs, interventions, and outcome measures,

a quantitative meta-analysis was not feasible. Data were analyzed to address the study objectives regarding the efficacy of nerve adhesion barriers in enhancing structural organization, functional recovery, and adhesion reduction. The synthesis emphasized structural and functional outcomes, including nerve conduction velocity, myelin thickness, axon regeneration, sensory recovery, and perineural scar prevention, providing a comprehensive overview of the effectiveness of each material.

Results

Study Selection

A literature search of the four databases yielded 549 hits. After removal of 10 duplicates, 539 titles and abstracts were screened to exclude 527 irrelevant papers. Of the remaining 12 papers, only 1 was excluded, and the rest underwent full-text review. Only five studies met the inclusion criteria and were included in narrative data synthesis. A summary of the study selection process is presented in the PRISMA flow diagram (Figure 1).

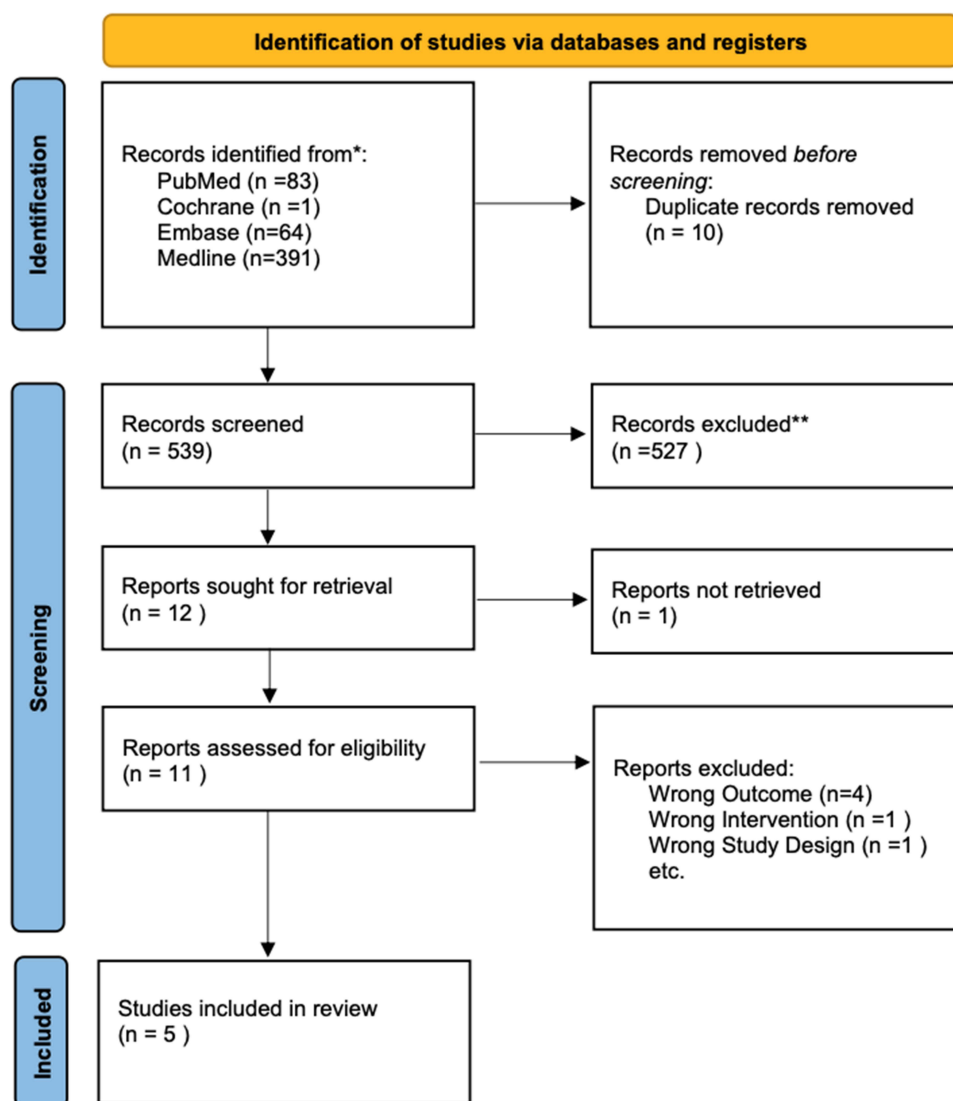


Figure 1 The PRISMA flow diagram of this study. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/register). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.

Study Characteristics and Risk of Bias

The five included studies were experimental in design, consisting of four animal studies and one randomized controlled trial involving human participants. Five different nerve adhesion barrier materials were evaluated: poly PDLLA, chitosan combined with hyaluronic acid, viscous pure alginate sol, an antiadhesive agent, and glutaraldehyde-crosslinked cartilage acellular matrix (CAM) film. Animal studies have used rat models to assess the outcomes related to nerve structure, functional recovery, and antiadhesion properties. A study by Li et al was conducted in China using Wistar Rats with sciatic nerve injury. The intervention group received a PDLLA film application, and the outcomes were measured through histological evaluations and electrophysiological testing. This study was supported by the Science and Technology Research and Planning Project of Jilin Provincial Education Department. Li et al, 2017, another animal study from China, utilized 60 Sprague-Dawley rats divided into four groups to assess the chitosan/hydroxyapatite (HA) combination on sciatic nerve crush injuries. Outcomes such as scar thickness, myelin thickness, axon diameter, and nerve conduction velocity (NCV) were measured through histological and functional analyses. Nam et al conducted a double-blind randomized controlled trial in South Korea involving adult patients who underwent parotidectomy with preservation of the greater auricular nerve. Patients received an antiadhesive agent or no treatment, and sensory function was assessed over a six-month follow-up period. This research was supported by Daewoong Pharmaceutical Company, although the authors report no conflicts of interest. Ohsumi et al tested a viscous pure alginate sol in a rat model of neurolysis in Japan. This study focuses on the histological and biomechanical outcomes of perineural and perineural adhesions. Finally, Shin et al evaluated CAM films in a rat model of sciatic nerve injury. This study used histological and functional recovery assessments, including gait analysis, to evaluate nerve regeneration. The study's characteristics are listed in [Table 2](#). Using the SYRCLE risk of bias tool for animal studies, two of the animal studies showed low quality due to unclear randomization and lack of blinding, while the other two showed moderate and good quality. The use of objective measures, such as histology and electrophysiology, helped mitigate the detection bias. The human study by Nam et al had a low risk of bias owing to its randomized, double-blind design, and adherence to rigorous assessment protocols. Detailed assessment aspects are presented in [Table 3](#).⁴⁻⁸

Study Outcomes

The study outcomes across the included trials consistently evaluated structural and regenerative outcomes, functional recovery, anti-adhesion, and scar prevention in peripheral nerve injuries. The reviewed studies collectively demonstrated that nerve adhesion barriers contribute positively to both nerve regeneration and functional outcomes, although their effectiveness varies depending on the material used ([Table 4](#)). PDLLA films showed moderate improvements in structural alignment and motor function, although motor nerve conduction outcomes were limited compared with those of other materials. In contrast, chitosan combined with hyaluronic acid (HA) exhibited significant structural and functional improvements, with higher nerve conduction velocities and reduced scarring compared to controls, indicating that it is one of the more effective combinations for nerve regeneration. Viscous pure alginate sol effectively minimized perineural adhesion and promoted perineural repair without inducing inflammation, making it a strong candidate for adhesion-focused applications. Glutaraldehyde-crosslinked cartilage acellular matrix (CAM) has demonstrated superior outcomes in reducing collagen deposition and supporting both myelination and axonal regeneration, with notable improvements in gait and functional recovery. Overall, both the chitosan/HA and CAM materials were more effective in promoting nerve regeneration and functional recovery, whereas PDLLA and alginate sol had good antiadhesion roles, albeit with limited functional outcomes.

Discussions

These five studies investigated the rate of nerve regeneration and motor and sensory functions in patients with peripheral nerve injuries treated with a neural adhesion barrier. While four studies revealed nerve regeneration rates, only the study by Nam et al did not provide information on this metric. Among the four investigations that documented nerve regeneration rates, the analyses conducted by Li et al and Ohsumi et al did not present their findings in a statistical format. The type of neural adhesion barrier employed in the four investigations varied. A 2017 study by Li et al

Table 2 The Characteristics of Included Studies

Title	Author; Year	Study Location	Study Design	Study Characteristics			
				Utilized Nerve Adhesion Barrier	Characteristics of Study Population	Sample Size (n)	Mean Age, Years (SD)
Promoting peripheral nerve regeneration with biodegradable poly (DL-lactic acid) films ⁵	Li et al, ⁵ 2015	Changchun, China	Animal Studies (Wistar Rats)	Biodegradable poly (DL-lactic acid) films	Wistar rats	Control group (n=6) #1: Sciatic nerve transection and anastomosis group (n=8) #2: Sciatic nerve transection and anastomosis with 6mm artificial nerve conduits (n=8) #3: Sciatic nerve transection and anastomosis with 6mm biodegradable PDLLA films wrapping (n=8)	NA
Chitosan conduit combined with Hyaluronic Acid to prevent sciatic nerve scar in a rat model of peripheral nerve crush injury ⁶	Li et al, ⁶ 2017	Beijing, China	Animal Studies (Sprague-Dawley Rats)	Chitosan + Hyaluronic Acid	Sprague-Dawley Rats	Chitosan group (n=15) Chitosan/HA group (n=15) Control group (n=15) HA group (n=15)	NA
Effect of glutaraldehyde-crosslinked cartilage acellular matrix film on anti-adhesion and nerve regeneration in a rat sciatic nerve injury model ⁴	Shin et al, ⁴ 2021	Suwon, Korea	Animal studies (Sprague-Dawley Rats)	Glutaraldehyde-crosslinked cartilage acellular matrix film (CAM)	Sprague-Dawley Rats	CAM film group (n=26) Control group (n=26)	7-week old
Enhancement of Perineural Repair and Inhibition of Nerve Adhesion by Viscous Injectable Pure Alginate Sol ⁷	Ohsumi et al, ⁷ 2004	Tsu City and Okayama, Japan	Animal studies (Lewis Rats)	Alginate Sol	Lewis Rats	Control (n=8) Intervention group (n=32): #1 Biomechanical analysis (n=16) #2 Functional Analysis (n=4) #3: Topical application (n=6) #4: Extensive internal application (n=6)	N/A
Effects of an antiadhesive agent on functional recovery of the greater auricular nerve after parotidectomy: a double-blind randomized controlled trial ⁸	Nam et al, ⁸ 2019	Seoul, South Korea	Double-blinded RCT	Mediclore®; Daewoong Pharmaceutical, Korea	1. Older than 18 years 2. Undergoing partial parotidectomy for benign salivary gland tumors 3. Consented to participate	Control (n=34) Intervention (n=46)	53.75 ± 13.19

Table 3 Quality Assessment of Studies Using the SYRCLE's and Cochrane-RoB Tool

	Selection			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Others	
Articles	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding operation	Random outcome assessment	Blinding outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Decision
Li et al, ⁵ 2015	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	No	No	Moderate Quality
Li et al, ⁶ 2017	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Good Quality
Shin et al, ⁴ 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	No	No	Low Quality
Ohsumi et al, ⁷ 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	No	No	Low Quality
Articles	Randomization Process		Deviations from the intended interventions		Missing outcome data		Measurement of the outcome		Selection of the reported result		Overall bias
Nam et al, ⁸ 2019	Low Risk		Low Risk		Low Risk		Low Risk		Low Risk		Low Risk

Table 4 Outcomes of the Included Studies

Author; Year	Nerve Regeneration Rate				Motor/Sensoric Function			
	Parameter	Control	Intervention	p	Parameter	Control	Intervention	p
Li et al ⁵ 2015	Histological Evaluation	Twisted nerve fibers and displayed irregular arrangement	Twisted nerve fibers and displayed irregular arrangement	NA	Motor Nerve Conduction Velocity	Control group: 24.8 ± 5.12 m/s Group I: 14.5 ± 2.89 m/s	16.9 ± 4.28 m/s	N/A
					Tibialis and gastrocnemius muscle wet weight	Control group: 24.8 ± 5.12 m/s Group I: 14.5 ± 2.89 m/s	0.48 ± 0.05%	N/A
Li et al, ⁶ 2017	Histological Evaluation	Higher quantification of epineurium collagen thickness in control group vs treatment groups		<0.05	Nerve Conduction Velocity	NCV in control group was significantly slower compared to all treatment groups		<0.05
		Arranged in an organized way but relatively sparsed, axons are the most irregular	Chitosan/HA: Most orderly arranged myelinated nerve fibers	NA	Nerve Conduction Amplitude	NCA in control group was significantly smaller compared to all treatment groups		<0.05
		Transmission Electron Microscopy						
	Myelin sheath thickness	4 weeks: no obvious difference 8 and 12 weeks: myelin sheath thickness in chitosan/HA group was slightly but significantly larger 12 weeks: thickness of myelin sheath was larger in all treatment groups in comparison to control groups						
	Nerve fiber number	4 weeks: no obvious difference 8 and 12 weeks: nerve fiber number in Chitosan/HA group was significantly larger compared with the control group	<0.05					
	Myelinated nerve fiber diameter	4 weeks: no obvious difference 8 and 12 weeks: myelin sheath diameter in control group was significantly smaller	>0.05					

Shin et al, ⁴ 2021	Histological Evaluation (Immunohistochemistry)	GAP-43 expression: 4 weeks: increased in both groups 8 weeks: decreased slightly in both groups 12 weeks: hardly visible no visible difference in GAP-43 expression		N/A	Video Gait Analysis			
		NF expression: 4 weeks: no significant changes 8 weeks: Increased in CAM-film 12 weeks: Increased in CAM-film						
	Myelinated axons (Toluidine blue staining)	1550 ± 101	1930 ± 99	0.028	Mean ankle angles	4 weeks: 56.4 ± 4.7 degrees 8 weeks: 54.2 ± 2.2 degrees 12 weeks: 53.7 ± 4.6 degrees	4 weeks: 66.8 ± 1.7 degrees 8 weeks: 82.9 ± 2.4 degrees 12 weeks: 65.0 ± 6.2 degrees	N/A
Width of nerve fibers	No significant differences were observed		N/A	Mean ankle angles at toe-off	4 weeks: 74.3 ± 3.7 degrees 8 weeks: 86.4 ± 3.7 degrees 12 weeks: 76.7 ± 3.6 degrees	4 weeks: 69.3 ± 2.3 degrees 8 weeks: 92.1 ± 4.1 degrees 12 weeks: 91.1 ± 5.7 degrees		
Ohsumi et al, ⁷ 2004	Histological findings	6 weeks post op: Control group: Surrounded by granulation tissue consisting of disorganized short collagen fibers and fibroblasts Intervention group: surrounded by compact bundles of long, thick collagen fibers, assumed to be a lamellar structure		N/A	N/A			
		Hematoxylin Eosin Staining Intervention group did not induce an inflammatory response						
Nam et al, ⁸ 2019	N/A				Sensory Evaluation	Improvements in tactile sensation and warm sensation in the ear lobule, and warm sensation in the mastoid area at 24 weeks post-op were greater in the study group than the control group	<0.05	
						No significant difference in QoL-related questions		>0.05

demonstrated the application of Chitosan combined with Hyaluronic Acid in animal trials. Histological examination indicated epineurial collagen thickness in the control group. This study indicated a notable variation in the quantity of nerve fibers following the application of a neural adhesion barrier composed of hyaluronic acid and chitosan. Similarly, a comparable study indicated negligible variation in the diameter of myelinated nerves. All four investigations documented nerve regeneration rates by histological evaluation, indicating reduced inflammation and collagen thickness relative to the control group. Overall, the nerve adhesion barrier demonstrated a better nerve regeneration ratio than the controls in all four studies.

Another indicator used to assess the nerve regeneration ratio in neural adhesion barriers is the quantity and dimensions of the nerve fibers. Li et al demonstrated that nerve repair membranes could enhance nerve regeneration by restoring the biological microenvironment. The study indicated that at 12 weeks post-surgery, there were increases in the number of myelinated nerve fibers, diameter of the nerve fibers, and thickness of the myelin sheath on the treatment side in comparison to the control group. A study by Li et al demonstrated that the width and thickness of myelinated nerve fibers yielded superior outcomes compared with the control group.⁹ A study conducted by Shin et al demonstrated that the diameter of myelinated axons was greater in the intervention group ($p = 0.028$), signifying a statistically significant outcome. The barrier approaches used in the experiments included biodegradable poly (DL-lactic acid) films, chitosan combined with Hyaluronic Acid, Glutaraldehyde-crosslinked cartilage acellular matrix film (CAM), and alginate solution. Benga et al found that hyaluronic acid, a fundamental component of the extracellular matrix, can enhance cell proliferation and migration, induce proliferation, chemotaxis, and phagocytosis in granulocytes, and promote degranulation and motility in macrophages. Multiple studies have indicated that the use of HA can diminish the development of adhesion tissue in the peripheral nervous system without suggesting any disruption in the wound healing process.¹⁰ Another study indicated that chitoooligosaccharides can facilitate nerve regeneration due to their antioxidative, anti-inflammatory, antiproliferative, and antibacterial capabilities, as well as their demonstrated neuroprotective effects.¹¹

The second criterion evaluated in this study was motor and sensory functions. Only one study, conducted by Ohsumi et al, did not evaluate motor and sensory functions. The measures for assessing motor and sensory functions included motor nerve conduction velocity, moist weight of the tibialis and gastrocnemius muscles, nerve conduction amplitude, and sensory evaluation. A study by Li et al indicated a modest increase in motor neuron conduction velocity, although no statistical statistics were provided. The study by Li et al indicates that nerve conduction velocity (NCV) in the control group was substantially slower than in all treatment groups, along with nerve conduction amplitude, with statistical significance ($p < 0.05$). Sensory evaluation showed an improvement in tactile sensation and warm sensation in the ear lobule and warm sensation in the mastoid area ($p < 0.05$).

Numerous investigations have demonstrated that adhesions surrounding peripheral nerves can induce symptoms in affected patients, hinder regeneration, and necessitate additional surgical interventions. Adhesions surrounding the nerve can compress it, hindering its critical gliding function and causing fibrosis in the neural and perineural tissues, which results in compromised nerve perfusion and delayed regeneration. A study by Schmid et al showed that wrapping with autologous or bioartificial material can create a barrier around the nerve, which prevents the formation of extensive scarring between the nerves using a synthetic collagen matrix. Kikuchi et al demonstrated that E8002, a new antiadhesive membrane containing l-ascorbic acid, could enhance motor function in a sciatic rat model by promoting fibrinolysis.^{12,13}

There is increasing interest in complementary and alternative methods to improve nerve regeneration and functional recovery, including regenerative scaffolds and electrical stimulation. Regenerative scaffolds can provide physical and metabolic assistance for neuron regeneration. These scaffolds can be engineered to replicate the natural extracellular matrix, facilitating an optimal environment for neuronal growth and differentiation. The integration of conductive materials into scaffolds can also promote electrical stimulation, hence augmenting regeneration potential.^{14,15}

Electrical stimulation (ES) has become increasingly recognized as a non-invasive or minimally invasive supplementary treatment for peripheral nerve injury (PNI). The utilization of electrical stimulation can augment nerve regeneration by facilitating axonal growth, regulating the inflammatory response, and enhancing blood circulation to the affected region. Elabd et al conducted a systematic analysis highlighting the significance of electrical stimulation in peripheral nerve regeneration, indicating that diverse stimulation protocols might produce advantageous results in both preclinical

and clinical contexts.¹⁶ Another study by Piccinini et al also shows the efficacy of electrical stimulation in enhancing nerve regeneration following surgical repair.¹⁷

Study Limitations

This systematic review included only five studies, four of which were animal studies and one was an RCT involving human participants, thus limiting the generalizability of the findings to broader clinical applications. The reliance on animal models may not fully capture the complexities of peripheral nerve injury and regeneration in humans. A single human study had a specific focus on sensory and nerve recovery in parotidectomy, which may not represent other types of peripheral nerve injuries. Additionally, while all studies evaluated structural and functional outcomes, variations in materials, methods, and outcome measures introduced heterogeneity, making direct comparisons challenging and limiting the potential of meta-analyses. Therefore, this study mainly reviews the potential and promising benefits of nerve adhesion barriers without thorough evidence on its' applicability in human studies. Rigorous long-term clinical trials are evidently needed prior to implementing this material in practice and guidelines. Further research should prioritize conducting large, high-quality clinical trials to validate the efficacy of nerve adhesion barriers in diverse patient populations. Additionally, long-term functional outcome studies are essential to assess not only immediate improvements in nerve regeneration but also the durability and clinical significance of these interventions over time.

Conclusions

This systematic review included five studies evaluating the efficacy of various nerve adhesion barriers in enhancing nerve regeneration and functional recovery in peripheral nerve injuries. The materials studied were PDLA, chitosan with hyaluronic acid (HA), viscous alginate sol, an antiadhesive agent, and cartilage acellular matrix (CAM), each demonstrated potential benefits, with chitosan/HA and CAM showing the most comprehensive improvements in both structural and functional outcomes. These materials are associated with reduced scar formation, improved nerve fiber alignment, and enhanced functional recovery metrics such as nerve conduction velocity and sensory function. However, heterogeneity in the study design, limited number of available studies, outcome measures, and predominance of animal studies limited the generalizability of the findings to clinical practice. Future high-quality, randomized controlled trials in human populations are needed to validate these results and establish guidelines for the clinical use of nerve adhesion barriers. Furthermore, standardized outcome measures and extended follow-up periods are essential for assessing the long-term efficacy and safety of these interventions. Additionally, future studies may attempt to observe the efficacy of adhesion barriers as an adjunct to other available therapies such as neurotrophic factors or stem cells.

Data Sharing Statement

The authors are willing to share the data collected in this study and the data will be available upon request to corresponding author.

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The authors declare no conflicts of interest regarding the publication of this paper.

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