

The Impact of Supplements on Recovery After Peripheral Nerve Injury: A Review of the Literature

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Abstract

Peripheral nerve injury (PNI) can result from trauma, surgical resection, iatrogenic injury, and/or local anesthetic toxicity. Damage to peripheral nerves may result in debilitating weakness, numbness, paresthesia, pain, and/or autonomic instability. As PNI is associated with inflammation and nerve degeneration, means to mitigate this response could result in improved outcomes. Numerous nutrients have been investigated to prevent the negative sequelae of PNI. Alpha-lipoic acid, cytidine diphosphate-choline (CDP Choline), curcumin, melatonin, vitamin B12, and vitamin E have demonstrated notable success in improving recovery following PNI within animal models. While animal studies show ample evidence that various supplements may improve recovery after PNI, similar evidence in human patients is limited. The goal of this review is to analyze supplements that have been used successfully in animal models of PNI to serve as a reference for future studies on human patients. By analyzing supplements that have shown efficacy in animal studies, healthcare providers will have a resource from which to guide decision-making regarding future human studies investigating the role that supplements could play in PNI recovery. Ultimately, establishing a comprehensive understanding of these supplements in human patients following PNI may significantly improve post-surgical outcomes, quality of life, and peripheral nerve regeneration.

Categories: Plastic Surgery, Integrative/Complementary Medicine

Keywords: peripheral nerve injury, small bowel surgery, postoperative pain, toxic optic neuropathy, neuralgia, vitamins, nerve conduction

Introduction And Background

The peripheral nervous system relays information between the CNS and the remainder of the nervous system outside of the brain and spinal cord [1]. The majority of peripheral nerve injuries (PNI) are secondary to trauma, surgical resection, or toxicity from local anesthetics. Regardless of the cause, severe neuropathic pain is one of the morbidities that can occur due to PNI. Either remove severe neuropathic pain or list the different morbidities that may be associated with PNI [2-5].

Following PNI, a cascade of inflammatory and ischemic molecular events occur in the proximal and distal nerve and can contribute to subsequent neuropathy [6]. PNI results in the formation of free radicals and the release of cytokines. Free radicals increase the permeability of cellular membranes and allow for the intracellular influx of calcium. This influx can lead to the destruction of neurofilaments and microtubules by activating proteolytic pathways [7]. If the free radical damage is allowed to proceed unmitigated, successful nerve regeneration will not occur, resulting in functional or sensory deficit or painful neuropathic pain. If there were means to decrease the inflammatory cascade and quell the free radical production, the extent of injury might not be as great, and recovery could be augmented. Interventions that prevent oxidative stress, neuroinflammation, and cellular injury could be utilized to achieve this. While alternative mechanisms of PNI secondary to surgical trauma may exist, free radical generation and oxidative stress are the most widely understood mechanisms that contribute to PNI at this time.

There is a paucity of human studies investigating nutrients and supplements that may aid peripheral nerve regeneration and recovery. However, animal studies show ample evidence that various supplements may improve recovery after PNI. A review published in 2018 discussed nutrients that may play a role in preserving nerve function and in augmenting recovery after PNI. Nutrients of interest included omega-3 and omega-6 fatty acids, B vitamins, antioxidants, minerals, phenolic compounds, and alpha-lipoic acid [3]. However, numerous supplements which were not previously reviewed in this publication have also demonstrated success in animal models post PNI. The goal of this review is to analyze supplements that have been used successfully in animal models of PNI to serve as a reference for future studies on human patients. By analyzing supplements that have shown efficacy in animal studies, healthcare providers will have a resource from which to guide decision-making regarding future human studies investigating the role that supplements could play in PNI recovery.

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Review

Methods

A PubMed, EMBASE, and Medline search was conducted using the key terms “antioxidant,” “vitamin,” “peripheral nerve injury,” and “sciatic nerve injury.” This search yielded a total of 96 relevant primary studies that pertained to PNI following surgery, from which data were extracted. Methods of PNI included nerve crush, constriction, ligation, and transection. Supplements with four or more citations will be discussed below in alphabetical order.

Results

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a powerful antioxidant and cofactor for many mitochondrial reactions. It is a scavenger of reactive oxygen species and is able to interact with and regenerate other antioxidants, such as vitamin C and E [8].

Six studies, all performed in rat models, addressed the role of ALA after PNI [9-14].

After PNI, ALA was able to increase levels of antioxidants [9], decrease oxidative stress [12], improve recovery of nerve function and conduction velocity [14] and the area of regenerating axon and myelin [13, 14]. Furthermore, given the well-established role of vitamin B12 in attenuating nerve damage in the CNS, some studies compared the efficacy of vitamin B12 and ALA in peripheral nerve regeneration. Compared to vitamin B12, ALA was more effective in improving sciatic functional index values [10] and restructuring the regenerating nerve [11].

Curcumin

Curcumin, the active ingredient of turmeric [15, 16], has been utilized for centuries to treat inflammatory diseases, pain, and trauma [17]. It regulates numerous cell-signaling pathways by modulating transcription factors and kinases for the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins [15, 17-20]. In the CNS, curcumin has a wide range of targets and provides numerous neuroprotective effects, including impacting neurotransmitters in the brain, regulating the hypothalamic-pituitary-adrenal axis, improving nerve regeneration, and inhibiting neuronal apoptosis [21-26].

Nine articles addressed the role of curcumin after PNI [27-35], all of which were conducted in a rat model except one mouse study [29].

After PNI, curcumin was able to reduce cell loss [27], improve the action, potential amplitude and conduction velocity [28], improve mechanical sensitivity [29], functional assessments [29, 31, 32, 35], motor and sensitive nerve conduction velocity [29], axonal regeneration [32, 34], myelination [29, 31, 33], and therefore improved the diameter of nerve fibers [31], reduce reactive oxygen species [29, 35], lipid peroxidation [29] and cell death [35], and expedite the reversal of mechanical allodynia [30].

Cytidine 5'-Diphosphocholine (Citicoline/CDP-choline)

Cytidine 5'-diphosphocholine, also known as Citicoline or CDP-choline, is a naturally occurring nucleotide that plays an essential role in phospholipid synthesis [36]. When provided exogenously, CDP-choline divides into choline and cytidine and serve as substrates for phospholipid synthesis [37].

CDP-choline is critical in establishing and maintaining cell membrane structure and protecting neurons during hypoxic and ischemic conditions [38].

Six articles addressed the role of cytidine 5'-diphosphocholine after PNI, all of which were conducted in a rat model [37, 39-43].

CDP-choline administration resulted in decreased scar formation and nerve adherence to surrounding tissue, improved sciatic nerve functional recovery, increased amplitude of the muscle action potential, axonal organization, axonal counts, axonal density, and axonal myelination following PNI [37, 39-43], and reduced neuropathic pain [42]. In addition, CDP-choline decreased levels of MMP-2 and MMP-9 and increased MMP inhibitors TIMP-1 and TIMP-3 [39].

Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is the main polyphenolic compound found in *Camellia sinensis*, also known as green tea. EGCG is a free radical scavenger, oxidative stress inhibitor, modulator of apoptosis, pro-oxidant, and anti-inflammatory agent [44-53].

Four articles addressed the role of EGCG after PNI [54-57]. Studies were performed in either rat or rabbit sciatic nerve crush [54,57], rat sciatic nerve transection [55], or rat vagus or hypoglossal crush models [56].

EGCG was able to improve the axonal and myelin regeneration, enhance functional recovery [54] and neuronal survival time after transection [55], reduce markers of oxidation [56], alleviate motor and sensory impairment, and improve neuronal regeneration [57].

Melatonin

Melatonin is secreted by the pineal gland at the base of the brain and it plays numerous roles in the human body, including regulating circadian rhythms, sleep physiology, mental status, reproduction, tumor development, and aging [58-60]. In addition, it acts as an antioxidant via a direct influence on toxic radicals and through the induction of enzymes that detoxify free radicals [7].

Thirteen articles addressed the role of melatonin after PNI [7, 61-72], all of which were conducted in a rat model except for two mouse studies [61, 62].

Melatonin improved structural preservation of the myelin sheaths [61], neural regeneration [72], functional outcomes [7, 65, 67], nerve conduction velocity [65], Schwann cell proliferation [64], axonal regeneration [66], increased malondialdehyde [62], decreased nerve peroxidation [63], and reduced oxidative stress [68, 71].

Quercetin

Quercetin, a plant flavonoid found in many fruits, vegetables, and aromatic herbs [73], is a powerful antioxidant, anti-angiogenic, anti-inflammatory, neuroprotective, and anti-apoptotic agent [73, 74].

Three studies addressed the role of quercetin after PNI; two were performed in mouse models [75, 76], and one each was performed in both mouse and rat models [77].

Quercetin enhanced axon remyelination, motor nerve conduction velocity, plantar muscle function [76], and nerve regeneration [77]. It was also found to be superior to gabapentin and morphine in alleviating mechanical and thermal hypersensitivity [75].

Vitamin B12

Vitamin B12 is a water-soluble vitamin obtained from dietary meat, eggs, dairy, and other animal-derived products [78]. The deficiency of vitamin B12 can result in neurotoxicity and contribute to the development of subacute combined degeneration, a disorder of the CNS characterized by sensory deficits, motor weakness, paresthesia, and gait ataxia [79]. In addition, within the peripheral nervous system, there is evidence suggesting that B vitamins play a role in peripheral nerve repair following insult [80].

Four studies investigated the role of vitamin B12 after PNI using rat models; two used vitamin B12 in combination with other vitamins [81, 82], and two investigated the role of vitamin B12 alone [80, 83].

Combined B-vitamin administration improved the toe-spreading reflex [81]. Compared to vitamin B1 and B6 alone, vitamin B12 was superior in augmenting peripheral nerve regeneration [80]. A combination of vitamin B12 and vitamin E acetate increased motor nerve conduction velocity and decreased the progression of thermal hyperalgesia following sciatic nerve crush injury [82]. At high doses, methylcobalamin, the active form of vitamin B12, accelerated nerve regeneration, increased myelination, and improved motor and functional recovery of injured nerves [80, 83].

Vitamin E

Vitamin E is an essential lipid-soluble vitamin with potent antioxidant effects. In addition to preventing free-radical reactions, vitamin E can act as a chain-breaking antioxidant that prevents lipid peroxidation [84].

Five articles addressed the role of vitamin E following PNI, all of which were conducted in a rat model [82, 85, 86] except one mouse study [87] and one cat study [88].

Vitamin E administration improved sciatic nerve function, increased the number of functional motor neurons, suppressed cold and mechanical allodynia, and decreased Wallerian degeneration, nerve gliosis, muscle atrophy, blood malondialdehyde levels, and injury-induced 4-hydroxynonenal activity [85,86]. When combined with selenium, it decreased the degeneration of motor nerve terminals and preserved the function of the motor nerve terminals within the soleus muscle [88]. While topical vitamin E alone improved functional sciatic nerve recovery, combined vitamin E and pyrroloquinoline quinone demonstrated significantly stronger benefits to vitamin E alone in nerve conduction velocity, functional motor recovery,

and nerve regeneration [87].

A summary of supplements with four or more citations is included below in Table 1.

Supplement	Outcomes	
Alpha-Lipoic Acid	-Increased levels of antioxidants [9]	
	-Improved sciatic functional index values [10]	
	-Aided in healing and remyelinating damaged nerves [11]	
	-Decrease oxidative stress [12]	
	-Prevented degeneration of both axons and myelin [13]	
	-Improved recovery of nerve function [14]	
	-Increased nerve conduction velocity [14]	
	-Reduced cell loss [27]	
	-Improved the action potential amplitude of the sciatic nerve [28]	
	-Increased conduction velocity of motor neurons [28]	
Curcumin	-Improved mechanical sensitivity [29]	
	-Improved motor and sensitive nerve conduction velocity [29]	
	-Improved functional assessments [29, 31, 32, 35]	
	-Improved axonal regeneration [32, 34]	
	-Increase nerve myelination and therefore the diameter of nerve fibers [29, 31, 33]	
	-Reduce reactive oxygen species, lipid peroxidation and cell death [29, 35]	
	-Expedited the reversal of mechanical allodynia [30]	
	-Decreased levels of MMP-2 and MMP-9 with increased levels of TIMP-1 and TIMP-3 [39]	
	-Decreased scar formation [37, 41-43]	
	-Decreased nerve adherence to surrounding tissue [37, 40-43]	
Cytidine 5'-diphosphocholine (Citicoline/CDP-choline)	-Improved sciatic nerve functional recovery [37, 40-43]	
	-Increased amplitude of the muscle action potential [37, 40, 41]	
	-Increased axonal organization [37, 43]	
	-Increased axons, axonal density, and axonal myelination [37, 39-43]	
	-Decreased neuropathic pain [42]	
	-Improved axonal and myelin regeneration [54]	
	-Enhanced functional recovery [54]	
	(-)-Epigallocatechin-3-Gallate (EGCG)	-Increased neuronal survival time after transection [55]
		-Reduced markers of oxidation [56]
		-Alleviated motor and sensory impairment [57]
-Improved neuronal regeneration [57]		
-Improved structural preservation of the myelin sheaths [61]		
-Increased malondialdehyde [62]		
-Improved functional outcomes [7, 65, 67]		
-Decreased nerve peroxidation [63]		
Melatonin		-Increased Schwann cell proliferation [64]

	-Increased nerve conduction velocity [65]
	-Increased axonal regeneration [66]
	-Reduced oxidative stress [68]
	-Improved neural regeneration [72]
Quercetin	-Alleviating mechanical and thermal hypersensitivity [75]
	-Enhanced axon remyelination [76]
	-Increased motor nerve conduction velocity [76]
	-Improved plantar muscle function [76]
	-Improved nerve regeneration [77]
Vitamin B12	-Augmented peripheral nerve regeneration [80]
	-Improved toe-spreading reflex when combined with B1 and B6 [81]
	-Increased motor nerve conduction velocity when combined with vitamin E acetate [82]
	-Decreased the progression of thermal hyperalgesia when combined with vitamin E acetate [82]
	-Accelerated nerve regeneration [80, 83]
	-Increased nerve myelination [80, 83]
	-Improved motor and functional recovery of injured nerves [80, 83]
Vitamin E	-Increased functional motor neurons [85]
	-Decreased nerve gliosis [85]
	-Improved sciatic nerve function [85, 86]
	-Reduced muscle atrophy [86]
	-Decreased blood malondialdehyde levels and injury-induced 4-hydroxynonenal activity [86]
	-Decreased cold and mechanical allodynia [86]
	-Decreased Wallerian degeneration [86]
	-Reduced degeneration of motor nerve terminals when combined with selenium [88]
	-Preserved soleus muscle motor nerve terminals when combined with selenium [88]
	-Increased nerve conduction velocity [82, 87]
	-Improved motor functional recovery [87]
	-Improved nerve regeneration [87]

TABLE 1: Summary of reviewed supplements.

Additional supplements whose roles have been investigated following PNI in animal models include Acetyl-L-carnitine [89], Achyranthes bidentata [90,91], Acorus calamus [92,93], Agmatine [94], Alstonia scholaris [95], Ascorbic Acid [96], Azadirachta Indica [97], Butea monosperma [98], Cannabis sativa [99], Catechin [100], Creatine [101], Crocetin (saffron) [102,103], Crocin [86,103], Diethyldithiocarbamate (DEDIC) [104], Elaeagnus angustifolia [105], Frankincense [106], Genistein [107, 108], Ginkgo biloba [109], Glycyrrhizin [110], Green tea [111], Hericium erinaceus [112], Hydroalcoholic extract of red propolis [113], Isoquercitrin [114], Lithium [115], Lumbricus extract [116, 117], Magnesium [118], Ocimum sanctum [119], Pralidoxime [120], Primrose oil [121], Propolis [122], Punica granatum L [123], Pyrroloquinoline quinone [87], Resveratrol [124,125], Radix Hedysari [126], Safranal [86], Salvia officinalis [127], Sesame oil [128], Selenium [88], Soy Phytoestrogens [129], Soybeans [130], Vitamin B1 [80, 81], Vitamin B6 [80, 81], Vitamin D2 [131], and Vitamin D3 [132, 133].

Discussion

PNI can have devastating complications, ranging from functional or sensory deficits to painful neuroma formation. However, numerous supplements have demonstrated success in animal models of PNI to mitigate the inflammatory response and improve regeneration.

One consideration when translating animal study to human research is to assess the role of a single supplement versus combination therapy. While animal studies have investigated both single supplement and combination therapy, this is not as easily replicated in human research. As numerous supplements have demonstrated success in animal models of PNI, it might stand to reason that the most efficacious approach in humans would be to utilize numerous supplements simultaneously. While this may result in beneficial outcomes, it would remain uncertain which supplement was responsible for the observed results and if the supplements had an unexpected synergistic effect. Despite this uncertainty, the majority of the supplements aforementioned have a low side-effect profile and are generally well-tolerated by humans. Thus, while not clearly delineating the mechanism of action, combination trials in humans may still prove to be the most efficacious approach to optimize results.

Furthermore, the timing of the intervention was noted to augment healing after PNI. While many of the animal studies reviewed deliver the intervention prior to PNI, this is not always feasible in humans. However, interventions prior to injury are possible in certain scenarios, including amputation with nerve transection and surgeries that have the potential for nerve injury, such as parotidectomy with facial nerve preservation. In these instances, preoperative supplementation might play a synergistic role in a meticulous surgical technique in hastening nerve regeneration/ healing and preventing untoward outcomes. It was beyond the scope of this review to discuss supplementation to augment nerve recovery after nerve grafting and repair, but this is another area that requires investigation.

Also, rodents are metabolically very different from humans. They have a greater amount of metabolically active tissues, such as liver and kidney, and a lesser amount of metabolically inactive tissues, such as bones [134-136]. This could influence the rate of metabolism of supplements. In addition, rodents have different microbiomes than humans as they coevolved with different pathogens [137]. This would impact how rodents respond to various medications and how supplements are metabolized in the gut. Additionally, nerve gaps in rats are very small compared to most human gap lengths, and axotomies in rats can undergo complete recovery, unlike humans [138]. Thus, while animal models can certainly provide valuable information, they need to serve as a nidus for further, well-done human research.

Conclusions

In summary, numerous antioxidant supplements have demonstrated success in improving recovery after PNI. The mechanism of action is typically mitigation of inflammation and reactive oxygen species production. While these should serve as a nidus for future human trials, there are many important considerations when translating these studies to humans. However, the arena of supplementation to improve PNI in humans is relatively unexplored and requires well-structured prospective studies.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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