

VITAMIN B COMPLEX AS A POTENTIAL THERAPEUTICAL MODALITY IN COMBATING PERIPHERAL NERVE INJURY

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Injuries of the peripheral nerves represent a large-scale problem in the modern world. They lead to significant consequences considering working ability and quality of life due to restricted recovery, especially of motor function. Different therapeutical approaches have been used in order to improve motor recovery. A significant number of studies showed some beneficial effects of different B complex vitamins on motor regeneration. Different experimental animal models were used in these studies, as well as within in vitro studies. In this paper, we will present the effects of B complex vitamin therapy on peripheral nerve regeneration after injury.

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Key words: peripheral nerve injury, motor recovery, therapy, B vitamins

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Introduction

Injuries of the peripheral nerves represent a significant problem in the modern world (1). The incidence of peripheral nerve injuries in developed countries is high, around 20 out of 100,000 people per year (2), which is around 300,000 injuries in Europe per year (3). After injury, damage to the motor, sensory or autonomic function of the nerve occurs, or in the worst case, the loss of all of these functions. Injuries may be caused by different causes, including bone fracture, ischemia, penetration of a foreign body, after infection, injection of narcotic drugs or after the use of drugs. The number of peripheral nerve injuries is constantly increasing due to the increase in traffic accident rates, industrial traumatism, and injuries at work. Trauma of the peripheral nerves results in a significant neurological deficit and almost always leaves a certain percentage of

disability (4, 5). Such a trauma most commonly occurs in young male subjects in their most productive age (6) and therefore creates major problems, since the recovery is slow and usually incomplete. These injuries often make it impossible for a person to return to their original job and are therefore significant as a major socio-economic problem. It is estimated that 2-3% of all injuries are peripheral nerve injuries (6, 7). Injuries of the nerves of the upper limbs are more common, and they usually affect n. ulnaris and n. medianus, while injuries of the lower limbs affect n. ischiadicus, n. peroneus, n. tibialis, and n. femoralis.

Peripheral nerve injury and animal models

Generally, peripheral nerves may be injured in closed or open injuries. Open violations are more frequent, even though closed injuries account for a significant percentage.

Based on the severity of an injury, there are several degrees of peripheral nerve injury. Seddon (8) concludes that three degrees can be distinguished to neuropraxia, axonotmesis, and neurotmesis. Neuropraxia is a physiological block of conductivity, where the nerve is anatomically and histologically normal. It occurs most often due to blunt trauma, stretching, compression, and ischemia. Recovery is complete and spontaneous. Axonotmesis involves breaking the continuity of the axon without damaging the trunk of the nerve. Recovery is spontaneous but time-consuming, surgery is not indicated. Neurotmesis is a lesion of axons and connective tissue, complete or incomplete. A surgical intervention is indicated with the aim of reconstructing the nerve. On the other hand, Sunderland (9) provides a

more precise division of the lesions at five levels, where II, III, and IV levels are comparable to axonotmesis.

In order to discover the mechanisms of successful and unsuccessful reinnervation, animal models are used (10). Additionally, dysfunction studies require appropriate and functionally applicable measurement methods. Finally, the fact should be considered that successful functional regeneration can depend on various factors in different experimental models.

The model of facial nerve injuries as a pure motor nerve model, the facial nerve model, over the past decade has enabled the collection of a large number of data on the cellular and molecular responses of motoneurons and their surroundings. (11). The disadvantage of this model is a low recovery rate after reconstruction (12).

Sciatic nerve is a mixed nerve, containing motor and sensory axons. Motor recovery after injury reaches a maximum of 40% of normal function. This fact, in addition to the fact that the assessment of motor function recovery is difficult, makes the model of sciatic nerve injury limited in assessing the recovery of motor function of the peripheral nerve (13). The disadvantage of this model is a high degree of complications such as automutilation, the appearance of skin ulceration and joint contractures, and therefore is not a good model for studying the recovery of motor function of the peripheral nerve (13).

Femoral nerve is a mixed nerve that contains motor fibers which innervate m. quadriceps femoris as well as sensory axons for skin innervation. After transecting the motor branch, there are equal chances to establish correct and incorrect reinnervation, so the model of femoral nerve injury is good for the analysis of recovery of the motor component of the nerve (2). There is also a pure motor nerve model, as shown in the study by Nedeljković and colleagues (14), in which the section of the femoral nerve motor branch (innervating m. quadriceps femoris) is performed at a distance from bifurcation, leaving a sensitive branch intact, in order to exclude the possibility of wrong sprouting of the axon from the motor to the sensitive part.

Peripheral nerve regeneration

The response of the peripheral nervous system to injury is the induction of a self-repair process, and this is an essential difference between the peripheral and central nervous system (15, 16). Repair can occur through remyelination, collateral sprouting distally from preserved axons and regeneration from the site of injury (17).

Peripheral nerve regeneration is a complex process of cell-molecular interactions and structural changes in the proximal and distal stumps of the injured nerve, subsequently providing a meaningful functional recovery for patients. The proximal part of the injured nerve undergoes Wallerian degeneration up to the first node of Ranvier and then each injured axon elaborates multiple daughter axons. At the same time, the distal part of the injured nerve undergoes the same process of Wallerian degeneration,

which is essential as a preparation phase for the axon regeneration process, in order to eliminate the molecules that could interfere with regeneration. Wallerian degeneration involves the invasion of macrophages that ingest myelin and initiate the Schwann cell mitosis. After the cytoskeleton and cell membrane are destroyed, Schwann cells degrade myelin. Further, after cleansing, the regeneration takes place from the proximal to the distal end of the nerve (18). Schwann cells help regenerating axons to cross the injury site from the proximal to distal part of the nerve. The exceptional ability of Schwann cells is the ability to change their phenotype and to dedifferentiate when they lose contact with axons. Therefore, after peripheral nerve injury, there is a reduced expression of molecular markers that are characteristic feature of mature Schwann cells. Between the first and fifth day after the injury, Schwann cells start to proliferate and the maximum of their activation is reached about the fourth day, and then decreases during the following weeks. This proliferation plays a key role during Wallerian degeneration (18). The secondary phase of proliferation takes place during the regenerative process. As they proliferate within the endoneurium membrane, Schwann cells form the Bungner bands, providing thus a favorable environment for axon regeneration. Denervated Schwann cells increase the expression of fibronectin, laminin, tenascin, and some proteoglycans, which form a favorable environment for axon elongation. They also increase the expression of several neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor, neurotrophin 4, glial cell-derived neurotrophic factor, and insulin-like growth factor 1. Schwann cells reduce the production of myelin proteins, as well as some other trophic factors (19). When reinnervation occurs, suppression of the expression of neurotrophic factors and their receptors occurs, and Schwann cells are in a steady state (20). A low level of functional recovery after the use of acellular nerve grafts for nerve reconstruction after transection indicate that active Schwann cells are crucial to axon regeneration. The capacity of Schwann cells to maintain pro-regenerative phenotype during long periods of time explains the limited capacity of chronic denervated nerves to maintain axonal regeneration, indicating the importance of early nerve reparation and strategies that could accelerate the recovery (21).

Treatment of peripheral nerve injuries

Peripheral nerves have an innate capacity for the induction of repair process. However, this capacity is limited and this process is seldom successful, and surgical intervention following injury is almost always required. Consequently, surgery is the first treatment for most peripheral nerve injuries and the current gold standard treatments are either direct microsurgical nerve repair or autologous nerve grafts. However, the regeneration of motor and sensory function often remains incomplete because full functional recovery is dependent upon many factors including the patient age, trauma location, injury severity, and presence of other diseases and conditions with an adverse impact on nerve regeneration.

Therefore, the development of alternative repair strategies that complement current established surgical procedures is needed (22). Additionally, although there are different animal models and studies of peripheral nerve regeneration process, the best treatment of peripheral nerve injury is still debated (23). Bearing in the mind all the above facts, the studies of the effects of neuroprotective agents that could potentially increase axonal regeneration following peripheral nerve damage, especially if axonal integrity cannot be preserved, are needed. Vitamins of the B complex are possible candidates because they are infinitely renewable and amenable to molecular manipulation. There are various additional therapeutic approaches in peripheral nerve regeneration, but this paper will describe the use of vitamins of the B complex.

B vitamins as potential treatment modality for repairing peripheral nerve injuries

Vitamins are dietary components which are necessary for life and play an important role in health. B vitamins act as coenzymes in a substantial proportion of enzymatic processes and play key interacting roles in the majority of cellular functions (24). According to that, B vitamins are important for normal functioning of the nervous system as well (25). Due to its positive effects on the nervous system, both central and peripheral, they are often used in the treatment of various pathological conditions of the nervous system (26, 27). In this chapter, the functions of B vitamins and some of their effects upon the nervous system will be presented.

Vitamin B1 (Thiamine) is essential for normal growth and development. It expresses a positive effect upon the digestive, cardiovascular, and, especially nervous system. Vitamin B1 deficiency in humans causes the occurrence of cardiovascular diseases (Beriberi) and neurological disease (Wernick-Korskoff syndrome, Parkinson and Alzheimer disease) (28).

Vitamin B2 (Riboflavin) is a water-soluble vitamin present in two coenzyme forms of riboflavin, flavin mononucleotide and flavin adenine dinucleotide, playing important roles in enzymatic reactions. Riboflavin exerts neuroprotective effects in some neurological disorders (Parkinson disease, migraine, and multiple sclerosis) through its role in some pathways such as antioxidation, myelin formation, mitochondrial function, and iron metabolism. Hoan and colleagues (26) have shown that vitamin B2 improved behavioral outcome and reduced lesion volume, edema formation, and GFAP expression following traumatic brain injury.

Vitamin B3 (Nicotinamide), in the form of coenzymes, participate in many important redox reactions of the cell metabolism, such as cell respiration, the oxidation energy important molecules, biosynthesis of fatty acid and steroids, as well as in the oxidation of glucose-6-phosphate into ribose-5-phosphate in the pentose path. Further, as a coenzyme, B3 is important in DNA replication and repair, as well as in cell differentiation. Nicotinamide shows some neuroprotective effects in animal ischemia models (29, 30).

Vitamin B5 (Pantothenic acid) represents a functional part of coenzyme A. Coenzyme A is important for the synthesis of fatty acids, cholesterol, and acetylcholine. Lack of vitamin B5 leads to peripheral nerve damage, referred to as „burning feet syndrome“ (31).

Vitamin B6 includes a group of related compounds: Pyridoxine, Pyridoxal, and Pyridoxamine. They are metabolized in the body to pyridoxal phosphate, which acts as a coenzyme in many important reactions in the blood, nervous system, and skin. In this way, vitamin B6 in amino acid metabolism is a rate-limiting cofactor in the synthesis of neurotransmitters, including dopamine, serotonin, γ -aminobutyric acid, noradrenaline and melatonin hormone (25). It is assumed that increased levels of pyridoxal can have neuroprotective effects (32).

Vitamin B7 (Biotin) plays a key role in glucose metabolism and haemostasis, including the regulation of hepatic glucose uptake, gluconeogenesis (and lipogenesis), insulin receptor transcription, and pancreatic β -cell function (33). Therefore, vitamin B7 has influence to the brain that is particularly sensitive to the delivery and metabolism of glucose (25).

Vitamin B9 (Folate) and Vitamin B12 (Cobalamin) are inextricably linked due to their complementary roles in the “folate” and “methionine” cycles (25). Vitamin B12 is required for the normal functioning of the nervous system and its deficiency causes damage to white matter of the brain and spinal cord, resulting in peripheral neuropathy (34). It has been shown in vivo that vitamin B12 is the most effective of all B vitamins in the regeneration of peripheral nerve after trauma and reconstruction. Scalabrino and Peracchi (35) showed that methylcobalamin (MeB12), a methylated cobalamin analogue, promotes conversion of homocysteine to methionine and expresses a stronger affinity for nervous tissues than other analogues, including cyanocobalamin. That is why MeB12 is prescribed to ameliorate various neuropathies (36, 37). The positive effect of vitamin B12 includes several actions: (i) use of MeB12 promote neurite outgrowth, regeneration and conduction of nerves after trauma by the activation of ERK1/2 and Akt protein kinase (38); (ii) MeB12 promotes Schwann cell proliferation and migration (39), which is essential in providing a permissive environment for axonal growth (36); (iii) MeB12 treatment enhances the final outcome of end-to-side neuroorrhaphy, but not the excessive enumeration of invading collaterals (40); (iiii) MeB12 boosts the maturation of ingrowing axons to establish an effective connection, so that larger axons tend to prevail as the rats' survival lengthens (40); (iiiii) it also enhances axon myelination. Liao and colleagues (40) showed that the mean value of axon diameters in their MeB12-treated group is more than doubled compared to PBS-treated animals.

Recently, the therapy with assorted combinations of B vitamins has been investigated as an efficient method for the treatment of peripheral neuropathies, neuroregeneration, particularly in the regeneration of injured nerves. Vitamins of the B group are widely used in the treatment of peripheral neuropathies. Spinal cord ischaemia may cause long-lasting neuropathic pain in addition to other severe

problems. The mechanisms underlying neuropathic pain remain elusive and effective treatments of neuropathic pain are currently unavailable. B vitamins, such as B1, B6 and B12, are capable of antinociception in experimental animals with acute and chronic pain evoked by electrical, chemical and thermal stimulation, primary neuronal injury and diabetes (41, 42, 43). In 2006, Caram-Salas et al. (42) showed that the combination of vitamin B1 and vitamin B12 (analog cyanocobalamin) and dexamethasone reduced spinal nerve ligation induced allodynia in rats (approximately 90%), indicating a synergistic interaction between either vitamin B1 or vitamin B12 and dexamethasone and suggesting a possibility of clinical use of these drugs in the treatment of neuropathic pain in humans. The combination of B1, B6, and B12 synergistically inhibited thermal hyperalgesia, and their repetitive administration produced long-term inhibition of thermal hyperalgesia and suggested possible clinical utility of B vitamins in the treatment of neuropathic painful conditions following injury, inflammation, degeneration or other disorders in the nervous systems in human beings (41). Jolivalt and colleagues (2009) (43) showed the positive effects of B vitamins cocktails (B1, B6 and B12) on functional and behavioral disorders of diabetic rats that suggested their potential for use in the treatment of painful diabetic neuropathy. In addition, studies demonstrated that certain B vitamins, especially B6 and B12, can protect neurons from certain injuries (44, 45). The dose of these vitamins is important as well. Okada and colleagues (38) showed that high dose vitamin B12 had the potential to treat peripheral nerve injury. Recent studies have suggested that the use of a vitamin B combination (B1, B2, B3, B5, B6, and B12) in high doses after the transection of motor branch of rat femoral nerve contributes to the prevention of damage progression on one hand, and on the other, it promotes and accelerates the regeneration of the damaged nerve, so that their application in the treatment of peripheral nerve injury is justified. The vitamin B complex therapy applied in high doses

immediately postoperatively leads to the reduction of muscle atrophy, improved recovery of EMG parameters, reduction of nuclear density of the injured nerve and appropriate muscle, which all lead to the improved recovery of peripheral nerve motor function (14). Some authors investigated the combination of vitamin B12 with Dexamethasone and showed that this combination promote (i) regeneration of myelinated nerve fibers; (ii) proliferation of Schwann cells, (iii) recovery of sciatic functional index and sensory nerve conduction velocity (46). In line with all these data is the paper showing that the tissue levels of vitamin B complex and vitamin B12 in the injured sciatic nerve were significantly greater at 1 and 12 hours after experimental nerve injury, while they were significantly lower at 7 days than in the control group (47).

Conclusion

The effectiveness of B vitamins, alone or in different combinations, in the treatment of central and peripheral nervous system injury has been increasing, highlighting its importance in the development of new researches. This review showed the efficacy of B vitamins in the neuroregeneration process, elucidating a possible therapeutic potential in the treatment of peripheral nerve injury. However, even with the evidence that B vitamins can act on different targets and accelerate nerve regeneration, additional validated evidence is required to determine more intrinsic mechanisms of B vitamins effects in different peripheral nerve injury models.

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Revijalni rad

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doi:10.5633/amm.2018.0214**VITAMINI B KOMPLEKSA KAO POTENCIJALNI TERAPIJSKI
MODALITET U LEČENJU POVREDA PERIFERNOG NERVA***Predrag Nedeljković¹, Sanja Dacić^{2,3}, Miljan Kovačević², Sanja Peković³,
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Povrede perifernih nerava predstavljaju problem velikih razmera u savremenom svetu. Posledice po radnu i životnu aktivnost su velike usled ograničenih mogućnosti za regeneraciju, pogotovo motorne funkcije. Različiti terapeutski pristupi su pokušali da poboljšaju rezultate motorne regeneracije. Značajan broj studija je pokazao povoljan efekat različitih vitamina B kompleksa na regeneraciju perifernog nerva. U navedenim istraživanjima su korišćeni različiti eksperimentalni animalni modeli, kao i *in vitro* studije. U ovom radu će biti prikazan uticaj terapije vitaminima B kompleksa na regeneraciju perifernog nerva nakon povrede.

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Ključne reči: *povreda perifernog nerva, motorni oporavak, terapija, B vitamini*