A Review of Cobalamin and Peripheral Nerve Regeneration

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Abstract

Peripheral-Nerve-Injury (PNI) is a serious clinical challenge, which triggers inflammatory cascade and destroys nerve structure. Peripheral-Nerves (PN) are built with capability to repair and regenerate; but process is slow. PNI severely affects normal life-style. Chronic stage of it often leads to disability and other complications. Systematic review of cobalamin and its role in repair of PNI was conducted from the literature published from January-2011 to December-2020. Authentic databases were used for collection of the literature, followed by data evaluation and tabulation. The vitamin-B12 (Cobalamin) is involved in various physiological and metabolic functions with an essential role in one-carbon metabolism. Cobalamin hunts-off free-radicals, provides defending shield to neurons; maintaining normal electrophysiological functions. Several studies demonstrated; large dose of cobalamin promotes PN regeneration by various chromo-chromosomal gene factors. Systemic administration of cobalamin results in resumption of action-potential. Hence, cobalamin is effective for PNI; whether related with diabetes, herpes, sciatica, neuro-spinopathy or piriformis syndrome.

Keywords:

Nerve-Injury; nerve regenerate; Cobalamin; neurons

1. INTRODUCTION

Central Nervous System (CNS) is connected with body tissues via Peripheral Nerves (PN) and every tissue of body is provided with peripheral axon which extends up to meninges of brain. (Günay *et al.*, 2021). PN are communication source between brain and rest of body tissues. (Yildiran *et al.*, 2020). PN are composed of various groups of axons; the fascicles are also called nerve fibers (Wang *et al.*, 2019). PN possesses both motor and sensory neurons; motor nerve axons are covered with myelin sheath (MS) while sensory neuron axons are without

MS.MS are fatty substances and are synthesized by Schwann-Cells (SC). MS functions as a insulating material over axon; enabling quick transmission of impulses.(Bota and Fodor, 2019) SC along with MS formation plays fundamental role as extrinsic factor in PN regeneration while Fibroblasts help in this process (Wang *et al.*, 2018).

Trauma of PN is a leading cause of PNI; it triggers complicated inflammatory cascade which ultimately destroys basic nerve structure causing impaired function and painful conditions (Albay and Kahraman Akkalp, 2020). Chronic condition often ends-up with disability and other complications (Ehmedah *et al.*, 2020, Huang *et al.*, 2016). Globally it has become a serious clinical challenge (Yan *et al.*, 2019). PNI severely affect normal life-style and work performance (Ehmedah *et al.*, 2020). PN are built with capability to repair and regenerate itself, but the process is quite slow and sometimes may not occur (Wang *et al.*, 2019). Sunderland in 1951 reviewed Seddon's three PNI categories and re-classified it into five different categories depending upon magnitude of damage (Wang *et al.*, 2019). Currently there is no established cure of this condition (Bota and Fodor, 2019).

Vitamin-B_{12} (Cyanocobalamin); a water-soluble-vitamin performs various physiological and metabolic functions. Its role is essential in photosynthesis where in one carbon makes six carbon; synthesizes essential amino-acids like methionine from homocysteine (Brito *et al.*, 2017). Cobalamin's structure contains "cobalt" in its center and is a key substance for maintaining PN normal electrophysiological functions (Gan *et al.*, 2014) (Gan *et al.*, 2014). Cobalamin hunts-off free radicals and provides defending shield to neurons (Liao *et al.*, 2013). Deficiency of B_{12} results in demyelination of nerves; peripheral neuropathy; sensation loss and fatigue (Sil *et al.*, 2018). Several experiments performed in PNI and have shown that Cobalamin promotes PN regeneration. Hence a substantial review is required of various experiments supporting Vitamin B_{12} in PN regeneration.

The purpose of current review was to collect the literature regarding of role of vitamin B_{12} (Cobalamin) in regeneration of peripheral nerves after injury. Additionally; this also addresses the most appropriate strategy to reduce the risk of PNI particularly with high risk of this condition like patients of diabetes mellitus.

2. MATERIALS AND METHODS

Data source:

Literature review of cobalamin and its role in repair of PNI was conducted from the last 10 years from January-2011 to December-2020. Google-scholar, Science-Direct, Springer, Pub-Med and National Library of Medicine were the databases used for collecting the literature related with cobalamin and nerve regeneration. More than 56 articles were downloaded. Abstracts were reviewed; 10 articles were rejected after careful review, followed by screening, detailed review was conducted on remaining articles. Results were evaluated and tabulated and conclusions were made. Articles were also evaluated for their quality in terms of type of journal, data collection methods, statistical analysis and interpretations.

Inclusion criteria:

Articles related with peripheral nerve trauma; peripheral nerve regeneration; peripheral nerve conduction loss; peripheral nerve anatomical structure; types of peripheral nerve injuries; role of cobalamin in nerve function; peripheral nerve injury treatment methods.

3. RESULTS AND DISCUSSION

Study type, findings in human or animal are tabulated. These findings are pertaining to the role of cobalamin (Vitamin B_{12}) on nerves after peripheral nerve trauma; peripheral nerve conduction loss; peripheral nerve injury and in peripheral nerve regeneration and nerve functions (Table – 1).

Table – 1: The role of Cobalamin and findings in different species

S. No.	Study Type	Findings	Trial in Specie
Sciatic Nerve Injury			
1	Sciatic nerve crush injury (Gan *et al.*, 2014)	Cobalamin contributed nerve regeneration and functional recovery.	Mice
2	Sciatic nerve injury (Sun *et al.*, 2012)	Dexamethasone and Cobalamin enhanced myelinated nerve fiber regeneration.	Rats
3	Sciatic nerve injury (Albay and Akkalp, 2021)	Cobalamin and Tocopherol improved functional recovery.	Rats
4	Sciatica nerve injury (Sayanagi *et al.*, 2020)	Cobalamin with polyglycolic acid tube filled with collagen sponge enhanced functional recovery.	Rats
5	Sciatica nerve injury(Sayanagi *et al.*, 2018)	Electrospun fiber sheet containing cobalamin revealed sensory recovery and remyelination.	Rats
6	Sciatic nerve injury and epineural anastomosis (Horasanli *et al.*, 2017)	Cobalamin and alpha lipoic acid promoted nerve regeneration.	Rats
7	Sciatic nerve injury (Miyamura *et al.*, 2019)	Electrospun nanofiber sheet containing Cobalamin regenerated PN and enhanced functional recovery.	Rats
8	Left sciatic nerve crush injury (Albay *et al.*, 2020)	Promote regeneration of injured ischiadic nerve.	Rats
9	Left sciatic nerve semi-injury (Wang *et al.*, 2015)	Cobalamin and cholecalciferol synergistically improve nerve healing.	Rats
10	Left sciatic nerve semi-injury (Wang *et al.*, 2015)	Cobalamin produces functional recovery of injured nerve.	Rats
Femoral Nerve Injury			
11	Femoral nerve injury (Nedeljković *et al.*, 2017)	Vitamin B complex improved motor nerve function.	Rats
12	Femoral nerve injury (Ehmedah *et al.*, 2020)	Vitamin B complex successfully produce myelination of unmyelinated neurons and suppress neurodegeneration.	Rats
Diabetic Neuropathy			
13	Diabetic polyneuropathy (Dominguez *et al.*, 2012)	Dexamethasone and Cobalamin enhanced myelinated nerve fiber regeneration.	Rats
14	Diabetic retinopathy (Reddy *et al*., 2020)	Reduced retinal hypoxia.	Rats
Other PNIs			
15	Ulnar and musculocutaneous nerve neuropathy (Liao *et al*., 2013)	Cobalamin enhanced functional recovery.	Rats
16	Tibial nerve crush injury (Tamaddonfard *et al.*, 2014)	Cobalamin produced functional recovery of tibial nerve.	Rats

17	PNI (Huang *et al.*, 2016)	Healing effect of Cobalamin produced when co-administered with neurite growth factor.	Human
18	Isolated cortical neurons and cell culture microfluidic chambers (Suzuki *et al.*, 2017)	Cobalamin promoted axonal outgrowth.	Rats
19	Crush-induced peripheral nerve injury (Altun and Kurutaş, 2016)	Cobalamin level significantly rises at injury site.	Rats
20	Constricted infraorbital nerve (Kopruszinski *et al.*, 2012)	Cobalamin reduced heat and cold hyperalgesia.	Rats
21	Corneal abrasion (Romano *et al.*, 2014)	Promote corneal re-innervation and re-epithelization.	Rats
22	Wobbler mouse model of Amyotrophic lateral sclerosis (Ikeda *et al.*, 2015)	High doses of cobalamin delayed progression of disease.	Mouse
23	Peroneal PNI (Chen *et al.*, 2015)	Improved neuropathic symptoms.	Human
24	Dorsal root ganglion neuron Schwan cell co-culture system (Nishimoto *et al.*, 2015)	Cobalamin facilitated nerve regeneration.	Rats
25	Neurospinal diseases (Sravani *et al.*)	Significant improvement in neural painful conditions.	Human
26	Adsorption of Graphene oxide on Cobalamin (Niu *et al.*, 2019)	Cobalamin significantly improved symptoms.	Human
27	Sub-acute herpetic neuralgia (Xu *et al.*, 2013)	Improved neuralgia symptoms.	Human
28	PNI (Solomon, 2016)	Muscular strength improved.	Human
29	Traumatic Brain injury (Wu *et al.*, 2019)	Cobalamin promote survival of nerve cell in traumatic brain injury.	Mice
30	Piriformis syndrome (PS)(Huang *et al.*, 2019)	Co-administration of Cobalamin and mannitol is useful in PS.	Human

The results indicate that at crush induced injury site; levels of cobalamin rise and it speeds up PN regeneration (Altun and Kuruta°, 2016). Cobalamin up-regulates various chromosomal gene factors that stimulate nerve regeneration (Gan *et al.*, 2014). Implantation of nano-fiber sheet containing Cobalamin facilitate nerve growth without showing any harmful effect (Suzuki *et al.*, 2017). Cobalamin in combination of non-steriodal anti-inflammatory drugs (Diclofenac/ Celecoxib) significantly reduce Wallerian nerve degeneration and resumed PN function (Tamaddonfard *et al.*, 2014). Cobalamin along with other B-complex vitamins have ability to provides benefit for PN regeneration (Ehmedah *et al.*, 2020). Alpha lipoic-acid (2mg/kg) and cobalamin (2mg/kg) collectively improve nerve structure regeneration (Horasanli *et al.*, 2017). Cobalamin protected from MS (Multiple Sclerosis) related nerve degeneration; the dose administered 1.5mg/kg as compared to 0.5mg/kg showed better results (Wu *et al.*, 2019). Followed by PNI; Cobalamin exhibits antioxidant, anti-apoptotic and anti-necrotic effects and it initiates myelination process (Albay *et al.*, 2020).

Implant of fabricated electro-spun nano-fiber containing Cobalamin at PNI site demonstrated PN regeneration (Suzuki *et al.*, 2017). Electro-spun sheet carrying Cobalamin administered at local injury site amplified nerve repair (Miyamura

et al., 2019). Cobalamin loaded with graphene oxide joined a gap in PN; process revealed faster resumption of action-potential and muscle-work (Niu *et al.*, 2019). Co-administration of Cobalamin and dexamethasone caused increased population of SC and myelination process (Sun *et al.*, 2012). Cobalamin possesses extra ordinary potential for corneal nerve re-innervation (Romano *et al.*, 2014). Wound dressings containing 100mcg of cobalamin in polycaprolacton/gelatin revealed significant wound healing (Farzanfar *et al.*, 2020). In a Novel method of staging prepared from silk fibers containing cobalamin was implanted sub-cutaneously in rabbit; this technique showed enhanced neuritic growth (Zhang *et al.*, 2019). Wobbler mouse having auto-somal trembling disorder were treated with high doses of cobalamin; in this experiment, Cobalamin not only prevent worsening of motor neuron related diseases but also contributed in increased number of musculo-cutaneous nerve fibers (Ikeda *et al.*, 2015). Dose of 1500ìgm/day remarkably improved neuropathic symptoms in Diabetic patients and symptoms did reappear even after 24 weeks of therapy gap (Dominguez *et al.*, 2012). A randomized controlled trial of Herpetic Neuralgia (HN) patients; treated with injectable/oral Cobalamin; subcutaneous administration of Cobalamin is comparatively productive in relieving painful conditions (Xu *et al.*, 2013). In a retrospective study; over fourteen patients suffering from various neuro-spinal ailments received higher doses of the cobalamin intravenously for one month; results reflected profound effects in neuro-spinal conditions, diminish pain and improved physical and mental wellbeing (Sravani *et al.*). Diabetes induced rats treated with cobalamin revealed that it avoids retinal thinning while protecting rhodopsin in diabetic rat eyes (Reddy *et al.*, 2020). A clinical study screened patients (n=150) with PNI and administered intravenous 0.5mg of Cobalamin along with a Nerve Growth Factor (NGF); results displayed significant PNI functional recovery (Huang *et al.*, 2016). Using ultrasound machine technique as a guide to inject 500mcg dose of Cobalamin at peroneal nerve injury site consecutively for three months resulted in significant muscle strength (Chen *et al.*, 2015). 83% patients reported improvement in their neuropathic conditions after receiving 2mg of cobalamin IM/oral thrice a week for two consecutive weeks (Solomon, 2016). Co-administration of vitamin E and Cobalamin appeared to be fruitful in avoiding oxidative damage and neuropathic complications related to PNI (Morani, 2012). Mannitol infusion (20%) for five days and B-Complex (B_1,$B_{2,}$,$_{12}$) for six weeks administered continuously to PS (Pulmonary Stenosis) diagnosed patients; exhibited reduced PS (Huang *et al.*, 2019). A Twelve month study on patients associated with amyotrophic lateral sclerosis received large doses of intramuscular Cobalamin 25/50mg showed significant extended patients survival rate and protected further nerve damage (Kaji *et al.*, 2015).

4. CONCLUSION

Cobalamin is safe and effective in nerve regeneration, repair and maintenance of neural electrophysiological functions. However, the mechanism of nerve regeneration and neuro-protective role of cobalamin further needs to be elucidated at molecular and genetic level.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

None.

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