Section: Miscellaneous

Review Article

PREVALENCE OF LOW BACK PAIN AND TREATMENT OF LOW BACK PAIN WITH METHYLCOBALAMIN

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ABSTRACT

Chronic low back pain is the one of the most frequent causes of disability and morbidity in Indian context. Inactive forms of vit B12 are cyanocobalmin (CNCbl) and hydroxycobalmin (OHCbl). On Other side two adenosylcobalmin (AdoCbl) and Methylcobalmin are active in Mammalian cells. One of the potential activated form of vitB12 is methylcobalmin (MeCbl) used treat nervous disorders like Alzheimers and rheumatoid arthiritis in clinic.Day today one of the most health concern is back pain. Nearly 70-80 percent of adults suffer from lower back pain in a few times in their life. MeCbl promotes the rejuvenation of injured nerves, develop nerve conduction and inhibits ectopic spontaneous discharges from the injured primary sensory neurons. Food proteins namely methionine synthase and methyl malonic acid mutase contains rich amount of vit B12. Cooking food release these enzymes and further makes active vit B12 into non functional form and destroy it. This narrative review summarizes the potential uses of Methylcobalmine(MeCbl) in lower back pain. The main objective of this review was to reveal the potential uses of MeCbl in lower back pain.

INTRODUCTION

Globally low back pain affected 619 million people in year 2020. One of the most frequent causes of diability and morbidity is low back pain. In recent years several hypothesis have been anticipated to explain the pathogenesis of low back pain and most of them focus on the dysfunction of spinal column and its components,[1] such as injury, spinal column degeneration,[2] and inferior facet-tip impingement of lamina,[3]and schomrl's nodes,[4] and and facet joint injury.[5] There are few researches up on nutrients role in repair of spinal nerves damage and regeneration. The main nutrient that required for nerves repair is vitamin B12. There are four forms of vit b12. Among them the active form of vitamin B12 is methylcobalmin(MeCbl) and it was considered as pain killer vitamin from 1950.All the way through body of methylation events methylcobalmin(MeCbl) acts as catylyst in formation of myelin protein in myelin sheath. Cobalamin plays important role in myelination of both peripheral and central nervous system and its insufficiency leads to demyelination in dorsal and lateral columns.MeCbl develops nerve conduction velocity (NCV), provokes Schwann cell differentiation and increases the secretion of brain-derived neurotropic factors (BDNFs) all of which contributes to axon regeneration.[6] In peripheral nervous system Schwann cells and Glial cells are important cells to form myelin. MeCbl confront glutamate-induced neurotoxicity and gives neuronal protection in injury.[7,8]MeCbl is essential to maintain the normal function of nervous system and its insufficiency leads to subacute degeneration of the spinal cord.[9] Across the globe one of the leading causes of disability in any profession is low back pain. Based up on distribution of pain the classification of low back pain done as axial (pain generally localized to low back pain) or radicular pain (pain radiating to lower extremities) is particularly relevant to clinical practice because commonly arise disease process involving lumbar spine.[10] In adults recent study shows pyschological distress, sedentary lifestyle and decreased physical activity are the factors that increase the intensity of low back pain.[11] Neurological vitamin b12 insufficiency results in axon degeneration of nerves of spinalcord. The deficiency of vitamin b12 results patchy, diffuse and progressive demyelination. The main objective of this review was to reveal potential use of MeCbl in chronic back pain. Epidemiological

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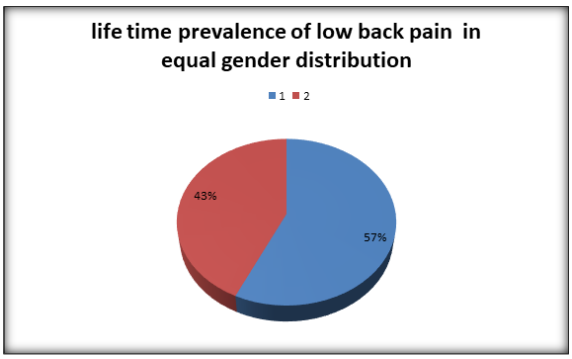
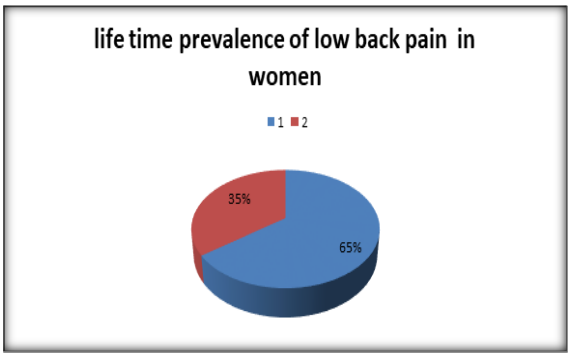
and community based study shown that the prevalence of low back pain is high in north India depicted in figure 1 which affects quality of life in respondents, the life time prevalence of low back pain in women is higher than men depicted in figure 2.[12]



In Figure 1: Blue indicates life time prevalence of low back pain in equal gender distribution. Red indicates population who never had episode of low back pain



In figure 2: blue indicates life time prevalence of low back pain in women is higher in contrast with men. Redindicates women population who never had any episode of low back pain.

Sources and absorption of vitamin B12

Dietary intake of functional form and sources of vit b12 are important measures to rejuvenate the injured nerves of spinal cord. Increased physical activities with stress significantly affect chronic back pain and even sedentary lifestyle greatly increases the incidence of recurring low back pain. In sedentary life style group with metabolic syndrome were found significantly increased chance of developing nonspecific low back pain.[21]Eukaryotes encompass algae, fungi, protists, plants, animals and humans do not make vitamin b12.[13] Prokaryotes are the only organisms that can biosynthesizes vit B12. However, about a third of all bacteria and archae species are able to biosynthesize vit B12.[14,15] In animals vitamin b12 obtained from prokaryotes is stored in tissues by microbial interactions in the natural food chain. Accordingly principal sources of vitamin b12 are from animalorigin.[16,17] The most important animal sources are meat, milk, dairy products, fish, shell fish and eggs.[18,19] Vitamins b12 consider to a certain extent heat stable compared with other water-soluble vitamins. Vitamin B12 is stable during cooking meat in the form of gravy, liquids and drippings.[22] Functional loss depends up the type of processing and food preparation.[18,20] Absorption occurs with intrinsic factor; synthesized with the help of prokaryotes and parietal cells in the GIT, primarily in terminal ileum and later it is stored in liver.[23]

Physical and chemical nature of MeCbl

Methyl cobalmin (MeCbl) is only water-soluble vitamin that can be stored in the human body. The chemical structure of methyl cobalmin comprises a cobalt ion as the center of the structure, which binds to four nitrogen ions to form a corrin ring and the lower ligand of the cobalt ion (beta) binds to the nitrogen ion of the dimethylbezimidazole molecule.[24] The upper ligand (alpha) of the cobalt ion binds to different groups resulting in four analogs of cobalmin, namely cyanocobalmin, MeCbl, adenosylcobalamin (AdoCbl), and hydroxycobalmin (OHCbl).[25,26] The structure of vitamin B12 is shown in fig.1. Methyl cobalmin (MeCbl), hydroxycobalminand 5'-deoxyadenosylcobalmin (AdoCbl) are natural forms of vitamin B12.Cyanocobalmin is industrially produced. Chemically more stable form is cyanocobalmin in contrast with adenosylcobalmin, methylcobalmin and hydroxycobalmin.

Pharmacodynamics and Pharmacokinetics of MeCbl

1. Absorption of orally taken MeCbl

MeCbl when taken orally or ingested passes through numerous phases before reaching the target cells. In digestive tract, various binding proteins are intrinsic factor (IF), transcobalmin (TC-I), and heptocorrin (HC) involved in absorption of various forms of vitamin B12, includes MeCbl. HC molecules are present in the upper gastrointestinal system and through saliva were initially bind to MeCbl. The cobalamin-HC complexes are degraded in the ileum and the resulting free cobalamin complexes bind to the apical region of intestinal epithelial cells via the cubam receptor, allowing them to degrade through lysosomes by process endocytosis. The released free cobalamin molecules enter the cytosol and blood circulation via passive transport or multidrug resistance protein (MDRP).[26,27]MeCbl is hydrophobic in nature because of this reason it enter in to the cell via passive diffusion.[28]

2. MeCbl in blood Circulation

Transcobalamin I (TC-I), TC-2, and TC-III are three proteins involved in distribution of cobalamin in the blood stream. When enters the blood circulation, approximately 75-90% of MeCbl binds to non-specific TC-I, whereas the remaining binds with affinity to TC-II and enter into the cells.[26,27] Cobalamin analogs are removed from the tissues and blood stream through TC-III and eliminate in bile by sending them in to the liver.[29]

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3. MeCbl enters the cell

Multifunctional receptors are non specific such as hepatic-specific proteins and asialoglycoproteins on the cell surface facilitate binding to TC-I-MeCbl complexes and these complexes enter into liver cells for storage. Divergent feature of TC-II-MeCbl complexes can only enter the peripheral cells via the specific TC-II receptor (CD 320) or passive diffusion because of their hydrophobic nature.[30]In neuronal cells MeCbl uptake is higher than in other cells because presence of megalin receptors on the surface of neurons. These receptors are liable to TC-II. NRG-1 expression via the PI3-Kinase pathway controls activation of megalinreceptor.[31]

4. MeCbl degradation inside the targeted cell

Once when the TC-MeCbl complex undergoes degradation in lysosomes releases free MeCbl into the cytoplasm by membranes called ABCD4 (cblf) and LMBD1 (cblf). MeCbl reacts with Cblc protein, resulting in the liberation of methyl groups through dealkylation. Consequently, intracellular MeCbl formed from free cobalmin perform its functions.[26,27]It has been identified that NRG-1 exerts neuroprotective through activation of the canonical PI3K/Akt and protects the neurons from oxidative stress caused by different agents hydrogen peroxide, organophosphates and MPP+.[32]

5. Excretion of MeCbl

Liver stores 0.5-5.0 ug of ingested MeCbl daily. This stored MeCbl is then secreted in the bile and reabsorbed in ileal enterocytes. In intestinal tract any unabsorbed MeCbl from bile or food is primarily excreted in feces, resulting to an estimated daily loss of 0.1% of the body reserves. Injected and excess MeCbl in blood is eliminated in the urine.[33] Abnormalities in gene sequence affect the enzyme activity involved in absorption and the binding capacity of vitamin B12 to binding proteins in intercellular metabolism and during the process of distribution.[34]Mutations decrease the reactivity of the MeCbl cofactor to the binding site of methionine synthase.[35]

6. Vitamin B12 Deficiency

Food bound cobalamin malabsorption or hindered release of vitamin B12 from consumed food is prevalent and primary cause of vitamin B12 deficiency. Secretion of hydrochloric acid is reduced due to gastritis, achlorhydria, gastrectomy and usage of antacids and proton pump inhibitors (PPIs) as a result diminishing the liberation of vitamin B12 from dietary proteins. There is strong correlation between the use PPIs or histamine H2 receptor antagonists and vitamin B12 insufficiency. Vitamin B12 levels deficient due to pervasive utilization of acid suppressing agents. Studies also shown reduction of vitamin B12 levels within population due to the increased utilization of reverse osmosis (R.O) drinking water,[36] even though unidentifiedmechanism of action. One possible reason R.O water membrane removes cobalt which is an essential component of vitamin B12. Low mineralized water for longer duration consumption causes chronic atrophic gastritis which leads to vitamin B12 deficiency.

Cellular and molecular action of MeCbl in Neurological diseases

The two coenzymes of vitamin B12 present in the cell are namely AdoCbl and MeCbl. All over the body in methylation reactions MeCbl act as a catalyst.[37]Important enzyme for the conversion of homocysteine to methionine is methionine synthase in which MeCbl acts as methyl donor. S-adenosyl methionine formed from methionine is a key methyl donor in various methylation reactions in the body.[6]MeCbl enhances tau aggregation which has beneficial effect in treatment of neurodegenerative illness such as Alzheimers disease. MeCbl prevents fibrillation and aggregation by binding and caping the cysteine residues of tau protein.[38] In cancer patients using with vincristine sulfate and by giving single injection of MeCbl before and during the generation of neuropathic pain decreases thermal hyperalgesia and nerve damage.[39]Loss of intra-epidermal nerve fibers is decreased and the reductions of typical mitochondria are due to the reduction of nerve damage. Low back and lumbar stenosis syndrome inititated by prolonged compression of the dorsal root ganglion (DRG) can be relieved by taking Methylcobalmin. Neuropathic pain symptoms such as heat, cold and mechanical hyperalgesia are alleviated by oral administration of MeCbl at a dose of 15 ug/kg twice a day for 21 days. MeCbl promotes myelin basic protein formation (MBP) and lipid synthesis by blocking the Erk1/2 pathway results in development of Schwann cell. The thickness and density of the myelin sheath increases during remyelination in which both MBP and lipid synthesis are needed.[40]MeCbl accelerates the development of the restored motor units of the injured nerve in neurorrhaphy procedure model of the damaged musculocutaneous nerve, which results in greater conduction velocity and better synchronization. In the receiving nerve the axonal sprout growth is promoted by MeCbl through expression of neuron specific cytoskeleton molecule β III tubulin. The activity of Schwann cells increased because presence of adequate MeCbl, which are responsible for most of axonal degeneration-associated debris removal is done due to the presence of adequate amount of MeCbl through increased activity of Schwann cells.[41] Prospective, parallel group, double blind and randomized study done by Mitbielli MAN etal in contrast of vitamin B12 versus B-complex vitamins in treatment of low back pain; they found superior reduction of low back pain in group A i.e supplement vitamin B12 given the form hydroxycobalamin, in second group B supplemented B-complex vitamins with cyanocobalamin. Both groups showed improvement of scores in comparsion with pretreatment group.[42] One of the studies revealed that methylcobalmin treatment group shown decreased sprouting which results voltage gate sodium channels (VGSC) accumulation

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as an important indicator for cell degeneration.[43] Research conducted to assess the effect of methylcobalmin on VGSC expression and spinal nerve ligation-4 (SNL) in neuropathic animal model indicates down regulation VGSC, which reduces neuropathic pain.[44] Study conducted by Diamant et al analyzed correlation between pH and lactate levels in discs of patients with lumbar rhizopathy and found that low pH was caused by the increased lactate level due to enhanced anaerobic glycolysis within Nucleus pulposus which counteracts decreased nutritional diffusion, the pain will arise within tissues with low Ph.[45]MeCbl through methylation cycle increases Erk and Akt activities, therefore improves neuronal survival and neurine outgrowth. MeCbl promotes the recovery of the injured sciatic nerve and its functions.[46]

Table 1: Analysis of pharmacological effect and pain recovery after methylcobalamin treatment in various models neuropathic pain

Author's	year	study design	Animals and nerves involved	highlighted outcomes
Okada etal (45)	2010	Invitro and invivo	Rats, Transected injury of sciatic nerve	MeCbl through methylation cycle increases Erk and Akt activities therefore improves neuronal survival and neurine outgrowth. MeCbl promotes the recovery of the injured sciatic nerve and its functions
Liao etal (40)	2013	Invivo	Rats,Ulnar and musculocutaneous nerve involved which results neuropathy	The expression of growth associated protein in the musculocutaneous nerve increased by giving MeCbl which suggest's ingrowth of ulnar axonal sprouts in reactive schwamn cells environment
Xu etal(38)	2016	Invivo	Rats, chemicall vincristine sulfate induces neuropathy.	Vincristine sulfate induced neuropathy pain inhibited by using MeCbl by inhibition of NADPH oxidase activation.
Mibelli MAN etal(41)	2020	invivo	Male and female humans	Nucleotides cytidine and uridine associated with vitamin B12 (Hydroxycobalamin) versus B-Complex vitamins in treatment of low back pain
Mutiawati et al (43)	2021	Invivo	Rats, segmental SNL on spinal nerve	MeCbl downregulates / or inactivates VGSC on the nerve fibers therefore improves neuropathic pain symptoms.

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