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Email: admin@theantiseptic.in / subscription@theantiseptic.in www. theantiseptic.in

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GENERAL

Methylcobalamin in Clinical Practice

SANJAY AGRAWAL

INTRODUCTION:

Vitamin B12, an indispensable water-soluble vitamin, plays a crucial role in the production of red blood cells, DNA synthesis and neurological functions. It is predominantly found in animal-based foods such as meat, fish, milk, dairy products and eggs. Plant foods typically do not contain substantial amount of vitamin B12.[1]

Vitamin B12 is essential for three enzymatic processes: the conversion of homocysteine to methionine; the conversion of methylmalonic acid to succinyl coenzyme A; and the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, a process necessary for DNA synthesis and red blood cell production.

The term vitamin B12 includes a number of chemical compounds that contain a common corrinoid group, centred on the mineral cobalt and various ligands, such as cyano, methyl, adenosyl, and hydroxyl ligands. Methylcobalamin and 5'-deoxyadenosylcobalamin are the active vitamin B12 moieties utilized in the human body to catalyse specific enzymatic reactions.

METHYLCOBALAMIN: AN ACTIVE FORM OF VITAMIN B12

Methylcobalamin is also known as mecobalamin or methyl B12. Methylcobalamin is a potent and active form of vitamin B12. It differs from cyanocobalamin in that the cyano group at the cobalt is replaced with a methyl group.

Methylcobalamin is the most bio-available type of Vitamin B12.Results of 3 human studies found lower tissue retention of B12 as a result of supplementation with cyanocobalamin rather than with methyl, adenosyl or hydroxyl cobalamins. The urinary excretion of cyanocobalamin was also more as compared to others. The researchers concluded that the lower bioavailability of cyanocobalamin was due to its lower efficiency in cellular uptake[2]. Few researchers have shown concerns about cyanide accumulation in human tissues from long-term intake of cyanocobalamin from supplements and/or fortified foods[3]. These findings suggest that supplementation with any of the natural bioidentical forms of B12 (MethylCbl, HydroxyCbl or AdenosylCbl) is preferred instead of the use of cyanocobalamin, owing to their superior bioavailability and safety[4].

Methylcobalamin is the only form of vitamin B12 that can cross the blood brain barrier without biotransformation. Its methyl group stimulates serotonin secretion, a neurotransmitter which is responsible for mood enhancement and protects the brain from damage against excitatory neurotransmitters.

Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including methylation of a number of sites within DNA, RNA, and proteins. Inadequate function of methionine synthase can lead hyperhomocysteinemia, which has been associated with increased risk of cardiovascular and neuropsychiatric disorders.

METHYLCOBALAMIN : BENEFICIAL ACTIONS

A number of laboratory and clinical studies have shown that methylcobalamin has following beneficial actions:

- Promotes synthesis of healthy myelin
- Helps regeneration of injured nerves
- Analgesic action: Relieves nerve pain associated with nerve degeneration, nerve compression, nerve inflammation
- Anti-oxidant action
- Anti-inflammatory action

METHYLCOBALAMIN: CLINICAL EVIDENCE

Methylcobalamin has been in clinical use since the 1990s. Methylcobalamin therapy is found to be useful in prevention as well as treatment of vitaminB12 deficiency.

A number of clinical studies have demonstrated efficacy of methylcobalamin in the treatment of following neurological disorders:

- Diabetic peripheral neuropathy
- Chronic low back pain
- Radicular pain such as sciatica
- Carpal tunnel syndrome
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Bell's palsy
- Amyotrophic lateral sclerosis
- Autism

Dr. Sanjay Agrawal,
Leading Pharmaceutical Consultant and
Editor-in Chief of IJM Today
Post Graduation Diploma in Naturopathy and Yoga,
6/146, Malviya Nagar,
Jaipur -302017

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Major studies evaluating the role of methylcobalamin in various neurological disorders are summarized below:

DIABETIC PERIPHERAL NEUROPATHY (DPN):

A number of clinical trials have been conducted to study the role of methylcobalamin

in treatment of DPN, either alone or in combination with other treatments[5]. A meta-analysis of such clinical trials concluded that methylcobalamin effectively decreases pain scores, neuropathic disability score and the neuropathic total symptom score in patients with diabetic peripheral neuropathy[6].

HERPETIC NEURALGIA

In a randomized controlled trial, patients with herpetic neuralgia received either

injections of 500 µg of methylcobalamin or lidocaine subcutaneously, in 4 separate locations on the affected dermatome or oral methylcobalamin 500 µg 3 times

a day. While lidocaine and oral methylcobalamin had small but significant effects on pain, daily injections of methylcobalamin reduced pain by half or more, in 60% of subjects[7].

TRIGEMINAL NEURALGIA.

The pain of trigeminal neuralgia (TN) can be described as agonizing, paroxysmal and lancinating which may be activated by activities such as chewing, speaking, and swallowing. A clinical trial proved that the pain of TN patients was greatly alleviated in the methylcobalamin group[8].

LOW BACK PAIN

In a double-blind, randomised, controlled study,60 patients with chronic non-specific low backache were assigned to either methylcobalamin group or the placebo group. Of the 60 patients, 27 received the placebo injections and 33 were given methylcobalamin injections (500 mcg of methylcobalamin IM, three times a week) for two weeks. There was a significant improvement in the Oswestry Disability Index and Visual Analogue Scale pain scores in the methylcobalamin group as compared to the placebo group ($p< 0.05$). The active treatment reduced the disability score by 27% and the pain score by 31%. The study concluded that Intramuscular methylcobalamin is both an effective and safe method of treatment for patients with non-specific low back pain[9].

NECK PAIN

In a clinical trial it was shown that spontaneous pain, allodynia, and paresthesia of patients with neck pain were improved significantly in the methylcobalamin group, and the analgesic effect was more obvious with continued treatment with methylcobalamin[10].

BELL'S PALSY

A study suggested that methylcobalamin dramatically increases the recovery time for facial nerve function in Bell's palsy[11].

AUTISM

An open-label trial with the use of 75 mcg/Kg of methylcobalamin, twice daily, together with folinic acid, demonstrated improvement in autistic symptoms, glutathione redox status and expressive communication. Receptive, expressive,and written language showed marked improvements[12]..

Another study reported that a high dose of methylcobalamin, administered in syrup form, ameliorates the clinical and psychological status of autistic individuals, probably due to the improved oxidative status[13].

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

373 patients with ALS were randomised to receive placebo, 25mg or 50 mg of methylcobalamin for 182 weeks. Post-hoc analyses of methylcobalamin-treated patients diagnosed and entered early (≤12 months'duration) showed longer time intervals to the primary event ($p<0.025$) and less decreases in the ALSFRS-R score ($p<0.025$) than the placebo group. The study concluded that early treatment with methylcobalamin may prolong survival and retard symptomatic progression of ALS without major side effects[14].

Few small studies have also reported beneficial effects of methylcobalamin treatment in patients with fibromyalgia, mild cognitive impairment, dementia and dry eye disease.

METHYLCOBALAMIN : DOSAGE

Methylcobalamin can be administered orally, intramuscularly or intravenously. Positive clinical results have been reported, irrespective of the route of administration.

A therapeutic dose for methylcobalamin varies from 1500 µg to a maximum of 6000 µg per day. No significant therapeu¬tic advantage appears to occur from dosages exceeding this maximum dose. It is likely that beneficial physiological effects of methylcobalaminmay may occur at dosages as low as 100 µg per day, especially if this dose is given for long time[15].

METHYLCOBALAMIN: SAFETY

Methylcobalamin has excellent tolerability, whether given orally or parenterally.

Clinical studies using doses as high as 25-50 mg, given twice weekly, have shown that it is free from any serious side effects.

CONCLUSIONS:

Chronic neuropathic pain is closely associated with chronic neuroinflammation caused by nerve injury and impediments to remyelination. Methylcobalamin

targets this fundamental aspect of pathophysiology and offers an effective and safe treatment option. It reduces neuroinflammation by regulating NFκB activity in immune cells and neurons, which results in the reduction of TNF-α, IL-1β, and IL-6 levels and an increase in IL-10 levels. It also controls peripheral and ganglionic sensitization, which affects nerve impulse transmission by inhibiting the ion channel activation in neurons. In addition, it also modulates remyelination[16].

Methylcobalamin alone or in combination with other agents, produces analgesic effect in patients suffering from non-specific low back pain, neck pain, diabetic neuropathic pain, subacute herpetic neuralgia, glossopharyngeal neuralgia, and trigeminal neuralgia. The possible mechanisms include improved nerve conduction velocity, promotion of injured nerve regeneration and inhibition of ectopic spontaneous discharges from peripheral primary sensory neurons[17].

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CREATING AN "ADULT-LIKE" MATURE HUMAN CARDIAC TISSUE

Researchers in the Biomedical Engineering Department at UConn have developed a new cardiac cell-derived platform that closely mimics the human heart, unlocking potential for more thorough preclinical drug development and testing, and model for cardiac diseases.

The research, published in Cell Reports by Assistant Professor Kshitiz in collaboration with Dr. Junaid Afzal in the cardiology department at the University of California San Francisco, presents a method that accelerates maturation of human cardiac cells towards a state suitable enough to be a surrogate for preclinical drug testing.

"There is a very strong need to create human cardiac constructs for all sorts of applications. Small animal models just do not recapitulate human heart biology, and human samples are scarce," says Kshitiz. "This matters because all drugs need to be tested for their toxicity to heart. It is widely believed that a large number of them unnecessarily fail clinical trials because we do not have human samples to test them with."

Kshitiz and Afzal first identified the need to create a matured human cardiac tissue during their time together at Johns Hopkins Medicine.

"When methods were developed to differentiate human pluripotent stem cells to cardiac cells, it created a big hope that finally we will have human heart constructs to work with," said Afzal. "While it is straightforward to get human cardiac cells, they are similar to fetal cells. What we need is adult cells."

Cardiovascular safety is the number one cause for failure of preclinical drug development, and there is a long standing need to create human cardiac tissue models to test drugs for cardiotoxicity. Currently, the small animal heart models display vastly different biochemical, physiological, and genetic features from humans—making it difficult to replicate the human heart in preclinical studies. In particular, it is very difficult to perform metabolic assessment of current cardiac constructs. Heart beats continuously and is a highly metabolically active organ.

"Metabolic and redox maturation is critical for heart cells, and we are able to achieve it and possibly create a gold standard—fundamentally shifting our expectations of creating a metabolically mature cardiac tissue," the researchers said.

In the study, the researchers utilized the cardiac biology in an adult human heart to rapidly mature differentiated cardiac cells into a more adult-like state. Within 30 days, the researchers achieved cardiac cells that disp layed structural,mechanical, metabolic, and electrophysiological characteristics close to adult heart muscle.

The researchers are optimistic that this application will not only be used for preclinical drug testing, but can also be used in future precision disease modeling to study disease mechanisms and test for regenerative therapies. The researchers hope that the many drugs that fail unnecessarily due to non-human methods will be salvaged for cures for cancer, immune and neurological diseases. - **eMed@Contin-Cardiology Care**