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Research Paper

ANALGESIC EFFECTS OF VITAMIN B_{12}: A RECENT UPDATE

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Abstract

Vitamin B_{12} is an essential nutrient which is not synthesized in human and its deficiency causes anemia and neuronal dysfunction. Deficiency usually occurs due to dietary inadequacy or malabsorption of the component. Vitamin B_{12} has some analogs including cyanocobalamin (CNCbl), methylcobalamin (MeCbl), hydroxocobalamin (OHCbl), and adenosylcobalamin (AdoCbl). Vitamin B_{12} improved nerve conduction in either patients of diabetic neuropathy or streptozotocin-diabetic ratsand experimental acrylamide neuropathy also improved visual function, rheumatoid arthritis, bell's palsy, and sleep-wake rhythm disorder. Recently, vitamin B_{12} has been demonstrated to have potential analgesic effects on neuropathic pain in experimental and clinical studies. The objective of our present study was to assemble the information on potential analgesic effects from clinical trials on treatment of painfull conditions. Animal studies support the inhibition of cyclooxygenase enzymes and other pain-signaling pathways. Animal studies also revealed synergistic benefits of vitamin B_{12} combined with nonsteroidal anti-inflammatory drugs and opiates. Recently, clinical studies provide evidence for the effectiveness of vitamin B_{12} for the treatment of nonspecifc low back pain, neck pain, diabetic neuropathic pain, acute & subacute herpetic neuralgia, glossopharyngeal neuralgia, chronic postthoracotomy pain (CPTP), aphthous ulcers, tabes dorsalis. This review article may appraise the clinicians and general populations that considering the low incidence of side effects and overall safety, vitamin

B_{12} alone or incombination with other agents may be an altranative choice for pain treatment.

Key words: Vitamin B12, Cyanocobalamin, Methylcobalamin, Hydroxycobalamin, Pain, Neuropathy.

INTRODUCTION

Folate and vitamin B_{12} are essential nutrients which are not synthesized in human body and whose deficiency is considered a health problem worldwide as it results in anemia and neuronal dysfunction. Deficiency of vitamin B_{12} occurs due to dietary inadequacy or malabsorption of the component. Deficiency is accessed by measuring serum concentration of vitamin B_{12}. Deficiency is usually observed more in elderly, vegetarians and pregnant women. But complication usually arises due to pregnancy and ageing. Vitamin B_{12} (cobalamin) is a very large molecule which always bound to another molecular group in the body like- methylcobalamin (MeCbl) which is cobalamin with a methyl group and cyanocobalamin (CNCbl) that is cobalamin with a cyano group. So different forms of vitamin B_{12} are distinguished according to the molecule to which cobalamin is bound. Hydroxocobalamin (OHCbl), and adenosylcobalamin (AdoCbl) are also some other analogs of vitamin B_{12}. biologically Vitamin B_{12} functions as a coenzyme that promote the functions of other enzymes. The two specific forms of vitamin B_{12}, methlycobalamin and adenosylcobalamin are active like a coenzyme in the body**.** Cyanocobalamin and hydroxocobalamin converted in the body into those mentioned two forms which are not directly active but a useful precursors of the active coenzymes.

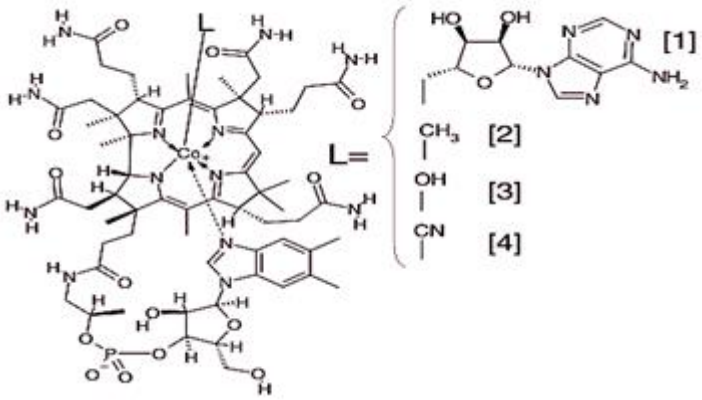

Figure 1: Structure of Vitamin B_{12} with its analogs

Vitamin B_{12} is regarded as a painkilling vitamin in some countries since 1950. Recent studies show that vitamin B_{12} plays a vital role in the normal functioning of the brain, nervous system and the formation of blood. It is normally involved DNA synthesis, fatty acid synthesis, and energy production [1]. In addition, methylcobalamin is the only form

of vitamin B_{12} that can cross the blood brain barrier without biotransformation. Its methyl group stimulates serotonin creation, which is a neurotransmitter and responsible for mood enhancement and protects the brain from damage. In recent year, vitamin B_{12} has been demonstrated to have potential analgesic effects on neuropathic pain in experimental and clinical studies.

EFFECTS OF VITAMIN B12 ON HUMAN TRIALS:

Researches showed that vitamin B_{12} has beneficial effects on clinical and experimental peripheral neuropathy. Vitamin B_{12} alone or incombination with other agents may be an altranative choice of analgesic agent considering its low side effects and overall safety.

Diabetic peripheral neuropathic pain

Neuropathy is one of the common complications of diabetes mellitus. Diabetic neuropathy is commonly thought to be related to the duration and severity of hyperglycaemia. However, it may also occur with hypoglycaemia. Clinical, symptoms in the legs, such as muscle cramps, burning pain, spontaneous pain, vibration sense, paresthesia, heaviness, and pain intensity were improved by vitamin B_{12} (as methylcobalamin or hydroxycobalamin) or its combination with other drugs (Figure 2). Furthermore, some researchers found that somatic and autonomic symptoms as well as nerve conduction velocity were improved by supplementation of vitamin B_{12} [1-3]. Commonly, more than 50% of patients with duration of diabetes of 25 years or more are affected, making it one of the most common diseases of the nervous system [4].

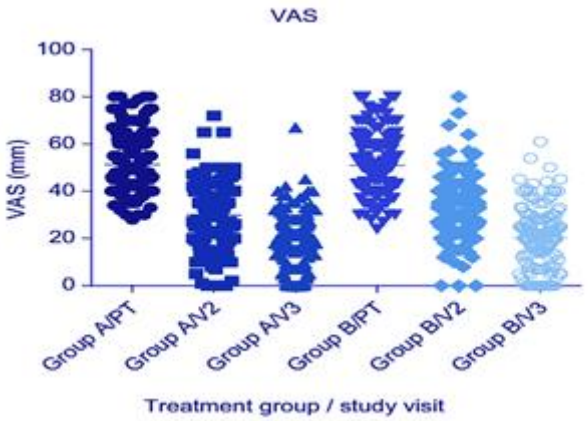

Figure 2: Visual analog scale scores for pain, for treatment groups A and B; Group A: subjects treated with uridine, cytidine, and vitamin B_{12}. Group B: subjects treated with vitamin B_{12} alone.
Note: PT=Pretreatment; VAS=Visual analog scale; V2=Visit two (after 15 days of treatment); V3=Visit three (after 30 days of treatment).

Low back pain and neck pain

vitamin B_{12} relief low back pain which is the second most common cause of disability in the US and costs 100-200 billion dollars per year in lost productivity, wages, and other costs [5]. Inflamed nerve that may cause low back pain are healed by the vitamin. Vitamin B_{12} strengthen and nourish the inflamed nerve . Between 50 and 80% adults have experienced low back pain at some time in their life [6], it is very common and MeCbl is thought to be becoming a decent choice for therapy of chronic low back pain [7]. Decreased low back pain was observed after supplementation of vitamin B_{12} [8]. In addition, improvement of nonspecific low back pain was observed by intramuscular supplementation of vitamin B_{12} [9]. Moreover, neurogenic claudication distance was improved significantly after the application of vitamin B_{12} [10] .Treatment with vitamin B_{12} shown to significantly improve spontaneous pain, allodynia, and paresthesia of patients suffering from neck pain. The analgesic effect was more obvious when treatment with vitamin B_{12} was increased [11].

VITAMIN B_{12} IN NEURALGIA

Acute and subacute herpetic neuralgia

Treatment with vitamin B_{12} significantly reduced continuous pain in patients with acute and subacute herpetic neuralgia [12] (Table 1). In addition, vitamin B_{12} signifcantly reduced pain and improved cutaneous healing of the affected area in ophthalmic herpetic neuralgia patients [13] (Table 1). Thus, vitamin B_{12} may be an alternative supplementation for management of herpetic neuralgia.

Glossopharyngeal neuralgia

In clinical practice, glossopharyngeal neuralgia (GPN) is a common facial neuralgia. Singh et al.reported that treatment with vitamin B_{12} combined with gabapentin and tramadol in GPN patients decreased pain intensity as well as improved pain relief [14] (Table 1).

Chronic Post thoracotomy Pain Syndrome

Chronic post thoracotomy pain (CPTP) or post- thoracotomy neuralgia is defined by the IASP as pain that recurs or persists along a thoracotomy incision for at least 2 months after the surgical procedure. Vitamin B_{12} incombination with Pregabalin reduced the chronic post thoracotomy pain with a high patient compliance [15] .

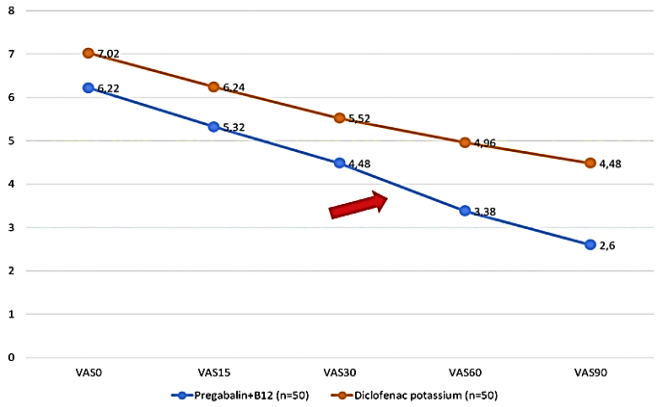

Figure 3: Vitamin B_{12} incombination with Pregabalin reduced the chronic post thoracotomy pain with a high patient compliance. Visual Analogue Scale (VAS) score changes during the treatment (Chronic Postthoracotomy Pain Syndrome). The red arrow indicates at what point these two curves become significantly different from each other.

Aphthous Ulcers

Aphthous ulcer is the most common oral mucosal lesion seen in primary care which occurs in up to ~2%-50% of the general population. A Randomized, Double-blind, placebo-controlled trial proved that pain of aphthous ulcers significantly relieved by vitamin B_{12} [16] (Table 1).

Tabes dorsalis

Tabes dorsalis is a clinical condition caused by demyelination in advanced syphilis (tertiary syphilis) which includes "lightning pains." Some patients reported highly significant pain reduction with injected vitamin B_{12} [17] (Table 1).

Neuropathic Pain of Animal Models

Combination of vitamin B_{12} and pioglitazone dramatically decreased allodynia and hyperalgesia in diabetic rats [18]. And the combined application of vitamin B_{12} and vitamin E alleviated thermal hyperalgesia in sciatic nerve crush injured rats [19]**.** Vitamin B_{12} in combination with thiamine (B_1), pyridoxine (B_6) significantly reduced thermal hyperalgesia in primary sensory neurons injury [20]. Some studies repoted that vitamin B_{12} was succesful in decreasing sprouting and given a positive impact on the reducing neuropathic pain of Sprague Dawley mice [21].

Anti nociceptive and antiinflammatiry effects of vitamin B12 in animal models

Some experimental evidence support that the administration of cyanocobalamin control acute and chronic neuropathic pain as well as inflammation [22]. In addition, formalin-induced muscle pain was significantly reduced by intracerebroventricular (ICV)

injection of vitamin B_{12} [23]. Combination of vitamin B_{12} with ketorolac shown to be more effective than those of their individual administration in formalin test [24]. Combined short term daily supplementation of vitamin B_{12} & FA is effective in lowering inflammatory pain & inflammation [25]. And also, significant decrement of nociceptive pain was observed after single supplementation of vitamin B_{12} in combination with vitamin B_1 and B_6 [26-30].

Table 1: The analgesic effect of vitamin B_{12} or combined use with other drugs on patients with neuralgia. [12-14,16,17]

Condition treated	Outcomes	Measures of intervention
Subacuteherpetic Neuralgia	Relieved pain	Subcutaneous injection of 1 mg MCB*daily for 4 weeks
Acute Herpetic Neuralgia	Reduced pain	IM methylcobalamin 1,000 μg in 2 mL combined with lidocaine 20 mg lidocaine injection for 14days
Acute Ophthalmic Herpetic Neuralgia	Improved cutaneous healing of the affected area, as well as a significant reduced pain	IM methylcobalamin combined with lidocaine injection for 14 days
Glossopharyngeal Neuralgia	Lowered pain intensities; improved pain relief; reduced pain interference with quality of life	Oral administration of gabapentin, tramadol, and MeCbl (0.5 mg)
Aphthous Ulcers	Relieved pain	Topical B_{12} ointment for 2 days
Tabes dorsalis is a condition caused by nerve damage from tertiary syphilis that includes "lightning pains."	Relieved lightning pains.	Daily intramuscular injections of B12 1,000 μg for 10 days followed by the same dose twice a week for 10 weeks.

DISCUSSION:

Vitamin B_{12} or its combination with other agents showed the potential analgesic effect in human and animal trals for example, nonspecifc low back pain, neck pain, diabetic neuropathic pain, acute & subacute herpetic neuralgia, glossopharyngeal neuralgia, chronic postthoracotomy pain (CPTP), aphthous ulcers, tabes dorsalis. However, it has been suggested that the analgesic effect of vitamin B_{12} may be improved nerve

conduction velocity as well as regenerate nerves by inducing axonal growth and schwann cell differentiation, which improves functional recovery in nerve crush injuries [31-34]. In addition, increasing inhibitory effects of afferent nociceptive neurons at the spinal cord levels along with decrease response of thalamic neurons to nociceptive stimulation by vitamin B_{12} [35]. Moreover, stimulation of vitamin B_{12} might release endogenous opioids or activate the opioid receptors as well as GABA metabolism, which in turn may reduce Ca^{2+} mediated release of neurotransmitters [30]. GABA might also enhance conductance through K^{+} channels and causes hyperpolarization of the postsynaptic membrane of the dorsal horn neurons, ultimately leading to decreased pain conduction [35,36]. Added to this, vitamin B_{12} may interact with the capsaicin receptor (TRPV1) and causes reduction in TRPV1 influx of positive ions finally decrease pain signaling [37]. This data may appraise the clinicians and general populations to use vitamin B_{12} along or with other agents for better management of pain.

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