

Update on the Use of Vitamin B12 in Management of pain

A. Abyad

Correspondence:

A. Abyad, MD, MPH, MBA, AGSF , AFCHSE
 CEO, Abyad Medical Center
 Chairman, Middle-East Academy for Medicine of Aging
 President, Middle East Association on Age & Alzheimer's
 Coordinator, Middle-East Primary Care Research Network
 Coordinator, Middle-East Network on Aging
Email: aabyad@cyberia.net.lb

ABSTRACT

Methylcobalamin (MeCbl), the activated form of vitamin B12, has been used to manage some nutritional diseases and other diseases in the clinic, including Alzheimer's disease and rheumatoid arthritis. As an adjuvant, it effects neuronal protection by fostering regeneration of injured nerves and alienating glutamate-induced neurotoxicity. Recently several studies revealed that MeCbl may have conceivable analgesic effects in experimental and clinical studies. It can reduce, pain behaviors in diabetic neuropathy, low back pain and neuralgia. MeCbl ameliorate nerve conduction, stimulated the regeneration of injured nerves, and inhibited ectopic spontaneous discharges of injured primary sensory neurons.

Low back pain is an everyday problem worldwide. It can lead to a great financial burden to society due to absenteeism or having work limitations. Back pain is one of the most common symptoms for seeing primary care physicians and one of the top 5 causes of surgery.

Recent studies have shown a correlation between vitamin B12 injection and a decrease in Low back pain. This review aims to synopsise the analgesic effect and mechanisms of MeCbl at the present with particular stress on chronic low back pain. Intramuscular vitamin B12 injections appear to be of benefit in the reduction of chronic low back pain and also improve associated disability. However, further research is necessary to study the possible long term adverse reactions of these intramuscular injections.

Key words: Vitamin B12, methylcobalamin, low back pain

1. Introduction

Vitamin B12 is essential for the health of our nervous system and blood cells, and vitamin B12 replacement is known for its role in the treatment of peripheral neuropathy and megaloblastic anemia (1).

Vitamin B12 is one of the body's main building blocks, assisting it to make DNA and keep nerves and blood tissue vigorous. Vitamin B12 is present in animal products, including beef, seafood, milk, and cheese. Therefore, vegetarians run the risk of having vitamin B12 deficiencies. Vitamin B12 is essential for prime health. Even in the absence of deficiency, shots of the vitamin have been considered recently as an alternative therapy for chronic conditions, including back pain.

Traditionally vitamin B12 had been used to treat anemic elderly patients and as an adjuvant in sport nutrition. It was considered as a painkiller since 1950 in some countries. Lately studies have shown that vitamin B12 played a major part in the normal functioning of the brain and nervous system and the formation of blood. Vitamin B12 is generally implicated in several metabolisms such as DNA synthesis and regulation, fatty acid synthesis, and energy production. Vitamin B12 has some analogs including cyanocobalamin (CNCbl), methylcobalamin (MeCbl), hydroxocobalamin (OHCbl), and adenosylcobalamin (AdoCbl). In mammalian cells, CNCbl and OHCbl are inactive forms and AdoCbl acts as a coenzyme of methylmalonyl Co-A mutase in mitochondria. However, vitamin B12 was not used directly in the human body, and it should be translated into activating forms such as MeCbl or AdoCbl. MeCbl differs from vitamin B12 in that the cyanide is replaced by a methyl group (2). It is a coenzyme of methionine synthase, which is needed for the formation of methionine from homocysteine in the methylation cycle which includes methylation of DNA or proteins (3-6). Compared with other analogs, MeCbl is the most effective one in being uptaken by subcellular organelles of neurons. Therefore, MeCbl can provide better treatments for nervous disorders through effective systemic or local delivery.

As a supporting agent, MeCbl has been forever used to manage several diseases, such as B12 deficiency and Alzheimer's disease syndromes (7, 8). L-methylfolate, MeCbl, and N-acetylcysteine ameliorate memory, emotional functions, and communication with other people among Alzheimer's patients (8,9). MeCbl also has neuronal protection embracing promoting injured nerve and axonal regeneration (10, 11) and antagonizing glutamate-induced neurotoxicity (10, 12). In addition, MeCbl amended nerve conduction in either patients of diabetic neuropathy (13-15) or streptozotocin-diabetic rats (16) and experimental acrylamide neuropathy (17). MeCbl also enhanced visual function (18), rheumatoid arthritis (19), Bell's palsy, and sleep-wake rhythm disorder (20, 21). Lately, MeCbl has been revealed to have possible analgesic effects on neuropathic pain in experimental and clinical studies.

2. The analgesic effect of MeCbl

MeCbl is one active form of vitamin B12 which can directly participate in homocysteine metabolism. Accumulating evidence is showing the beneficial effects of MeCbl on clinical and experimental peripheral neuropathy.

2.1. Diabetic Peripheral Neuropathic Pain

Paraesthesia, burning pains, and spontaneous pain in legs, were ameliorated by MeCbl (22,23) (Table 1). The effects of single use of MeCbl or combined use with other drugs were examined in diabetic neuropathy pain (13, 24) (Table 1 - next page). Clinical evidence showed that MeCbl had the ability to inhibit the neuropathic pain accompanying diabetic neuropathy.

The severity of the pain is variable and may be explained as a hot, burning, cold, aching, or itching sensation with, at times, increased skin sensitivity. It is a challenge in clinical practice to treat diabetic neuropathic pain. Several medications have been tried including Carbamazepine, and dolantin with no success. Similarly, therapeutic effects of aldose reductase inhibitors and nimodipine were not promising in clinic as much as basic studies showed. Fortunately, MeCbl may convey a sparkle of hope to treat diabetic neuropathic pain.

2.2. Low Back Pain

Back pain is one of the most frequent health complaints. It is a common complaint affecting 70-85% of people worldwide at some point during their life (25). The differential is extensive including, cancer, infection, inflammatory disorders, structural disorders of the spine itself, and disk herniation, are somewhat more common, and together account for back pain.

According to the WHO (World Health Organization), low back pain leads to a high economic burden due to the effects this often chronic problem has on work productivity (26). It is one of the most frequent causes behind visiting a primary care provider, and in the top five of the most common reasons for having surgery(27).

Initially, low back pain is usually managed with anti-inflammatories including non-steroidal, muscle relaxants, and narcotics. Persistent back pain is further treated with physical therapy, TENS units, massage, epidural steroid injections, and surgery. Treatment varies depending on the patient. The majority of patients recover within 12 weeks, while 10 to 20% endure low back pain past this time period, even with treatment (27,28). It emerges that vitamin B12 might be one of those additional treatment options.

The advantage of using B12 shots included decreasing the amount of non-steroidal anti-inflammatory drugs (NSAID), such as aspirin and ibuprofen. Vitamin B12 has no known side effects, according to the National Institutes of Health Office of Dietary Supplements, rivaled to long-term NSAID use, which may harm the gastrointestinal system and probably lead to heart attacks and strokes. Researchers aren't sure how vitamin B12 shots help patients decrease back pain. However, they anticipate that the vitamin helps nerves repair and regenerate in the back. Additional benefits to treating back pain with B12 shots include the vitamin's low cost, minimal side effects, and ability to get patients back to work and enjoying their lives.

Furthermore neurogenic claudication distance was ameliorated markedly after the application of MeCbl [29] (Table 2). However Waikakul's research showed that MeCbl was not good for pain on lumbar spinal stenosis [29]. In a trial, the analgesic effect of MeCbl has been examined in nonspecific low back pain patients with intramuscular injection [30] (Table 2 - page 35). The varying effect of MeCbl may be secondary to different causes of lumbar spinal stenosis and nonspecific low back pain. Additional studies are required to establish the effect of MeCbl on low back pain.

Three studies

Studies have shown that vitamin B12 shots can successfully decrease back pain.

One study conducted in 2000 by Italian researchers at the University of Palermo found that vitamin B12 helped to alleviate lower back pain. The study evaluated 60 patients aged between 18 and 65 with proven back pain lasting anywhere from six months to five years.

Study participants were divided into two groups and received either a B12 shot or a placebo. Results showed injections alleviated back pain in patients even if they entered the study with adequate blood levels of vitamin B12.

CHIU et al (31) conducted a randomized, double-blinded, placebo control study (5) to evaluate both the efficacy and safety of intramuscular methylcobalamin injections for treatment of chronic low back pain. Certain eligibility criteria were used for selection of the patient population. Included were patients who were between 20 and 65 years old and who had a history of low back pain, which had to be nonspecific in nature, and for greater than 6 months in duration. At the study's conclusion neither disability nor pain was meaningfully reduced in the placebo group. However, in the treatment group they estab-

Table 1: The analgesic effect of MeCbl or combined use with other drugs on patients with diabetic neuropathic pain

Effects of MeCbl	Indices	Measures of Intervention	Reference
Alleviation of neuropathic pain symptoms; Improved nerve conduction velocity	Pain scale scores of patients; measure of nerve conduction velocity	Oral administration of MeCbl for 3 months	Devathasan et al. [13]
Improved nerve conduction velocity	Measure of nerve conduction velocity	Intravenous administration of MeCbl	Ishihara et al. [15]
Improved the symptoms of paraesthesia, burning pains, and heaviness; no effect on nerve conduction velocity	Pain symptoms; measure of nerve conduction velocity	Repeated intrathecal injection of MeCbl at a high dose of 2.5mg/10 mL	Ide et al. [22]
Relieved spontaneous pain by 73%	Likert-type pain intensity scale; Patients' Global Impression of Change (PGIC) scale	Intramuscular injection of MeCbl for four weeks followed by oral administration of MeCbl for additional eight weeks	Li [23]
Relieved pain and paraesthesia; improved motor and sensory nerve conduction velocity	Neurological disability score for the grades of pain and paraesthesia	Intravenous injection of MeCbl for 6 weeks	Kuwabara et al. [14]
Reduced pain scores and good tolerance	Visual analog scale and chemical safety	Oral administration of immediate-release methylcobalamin and sustained-release pregabalin for 2 weeks.	Dongre and Swami [24]

lished a marked decrease in both disability and pain. These inferences were based on the ODI and VAS scores taken 2 months after initiation of treatment, see Table 2. Furthermore, the placebo group consumed significantly higher doses of paracetamol as compared to the participants in the treatment group; mean paracetamol consumption (in grams) was 87.6 ± 57.3 in the placebo group, 65.7 ± 75.2 in the treatment group. Treatment with intramuscular (IM) methylcobalamin had very few side effects, including hematoma and pain at the injection site. It is difficult to estimate any long term side effects since the duration of the study was short, 2 months.

MAURO et al (32) using a randomized, double blinded, placebo control study studied the efficacy of vitamin B12 in treating low back pain. Patients ranged between 18 to 65 years old with medical evidence of 6 months to 5 years of mechanical low back pain or sciatic neuritis. They also had to have at least 60 out of 100 on the VAS pain intensity scale at the start of the study. The total patients included were 60 patients. They were randomly allocated to either the placebo or the treatment group. The treatment group received Tricortin® 1000 2mL ampoules-containing 1000 mg vitamin B12, whereas the placebo group only received 2 mL ampoules of an unspecified injection.

Table 2: The analgesic effects of MeCbl on low back pain and neck pain in clinical trials

Effects of MeCbl	Indices	Measures of Intervention	Reference
Relieved spontaneous pain, allodynia, and paraesthesia.	Pain symptoms of patients with neck pain	Oral administration of MeCbl for 4 weeks	Hanai et al. [36]
Amelioration of neurogenic claudication distance; no effect on pain improvement and neurological signs	Pain symptoms; measure the neurogenic claudication distance of patients with degenerative lumbar spinal stenosis	Oral administration of MeCbl as an adjuvant medication for 6 months	W. Waikakul and S. Waikakul [29]
Reduced pain	Oswestry disability index questionnaire (ODI) and visual analogue scale (VAS) pain score of patients with nonspecific low back pain	Intramuscular injection of MeCbl for 2 weeks	Chiu et al. [31]
Pain and Disability	They also had to have at least 60 out of 100 on the VAS pain intensity scale at the start of the study	Intramuscular injection of MeCbl for 2 weeks	Mauro et al. [32]
Ameliorating nonspecific chronic low back pain, paraesthesia, & nocturnal pain as compared to placebo	Likert Scale	Intramuscular injection of MeCbl for 3 weeks	Abyad [32]

Table 3: The analgesic effect of MeCbl or combined with other agents on neuralgia

Effects of MeCbl	Indices	Measures of Intervention	Reference
Reduced or eliminated pain symptoms	Pain scales in patients with trigeminal neuralgia	Intravenous injection of MeCbl at a single dose of 0.5mg	Teramoto [39]
Relieved overall pain, continuous spontaneous pain, paroxysmal pain, and allodynia	Likert-type pain intensity scale; Patients' Global Impression of Change (PGIC) scale	Local subcutaneous injection of MeCbl for 4 weeks	Xu et al. [37]
Lowered pain intensities; improved pain relief; reduced pain interference with quality of life	Numerical pain scale and brief pain inventory of glossopharyngeal neuralgia	Oral administration of gabapentin, tramadol, and MeCbl (0.5mg)	Singh et al. [38]

Pain was evaluated with the VAS, a test in which the participants scored their pain on a scale of 0-100, where 0 meant no pain at all, and 100 was the worst pain one can have. In addition, the use of paracetamol was used to assess pain. Disability was assessed by using the DQ, a test that is made up of 24 questions and is then scored on a 0-24 scale. In both the placebo and treatment groups, pain and disability improved. In the placebo group, the VAS score declined from 70.63 ± 7.9 to 36.83 ± 27.4 , whereas in the treatment group it declined from 75.53 ± 8.9 to 9.53 ± 16.5 . The DQ score decreased from 11.53 ± 2.2 to 5.80 ± 3.3 in the placebo group and it decreased from 13.27 ± 2.7 to 2.43 ± 2.6 in the treatment group.

Nevertheless, there was a more statistically significant improvement in the treatment group. Paracetamol was used less in the treatment group. There were no reported adverse effects. Therefore, IM injection of vitamin B12 is safe in the short term. However, long-term effects of IM injections of vitamin B12 were not examined nor discussed in this study.

A study from Lebanon (33) examined the usefulness of cobalamin injection in lumbosacral disc disease in patients with mechanical or irritative lumbago. Over 4 years, a hundred and twenty patients with Lumbosacral disease were enrolled in the study. Patients' ages ranged between 18 to 65 years. The patients were divided randomly into treatment and control groups. Both groups received relative bed rest, NSAIDs and daily injection of vitamin B12 for the treatment group and sterile water for the control group. The duration of treatment lasted for three weeks, and the concentration of vitamin B12 was 1000 mg/ml. Patients were seen initially and at the end of treatment. Both treatment groups experienced a sharp decrease in pain and disability. However, comparison between groups at the end of the treatment period showed a statistically significant difference in favour of the active treatment both for pain, paraesthesia, and nocturnal pain. Consumption of paracetamol proved significantly higher in the placebo group than in the active treatment ($p < 0.0001$). The author concluded that intramuscular vitamin B12 injections seem to be effective at ameliorating nonspecific chronic low back pain as compared to placebo. Vitamin B12 injections also have exhibited only minimal side effects. There is a need for a larger study with longer duration that spans several years to assess the long-term side effects, especially as long-term effects can possibly be serious.

2.3. Neck Pain

Chronic neck pain is becoming a common problem in the adult population, with the prevalence of 30%-50% in 12 months [34, 35]. It was shown that spontaneous pain, allodynia, and paraesthesia of patients with neck pain were improved significantly in the MeCbl group, and with the increase of treatment time of MeCbl, the analgesic effect was more obvious [36] (Table 2).

2.4. Neuralgia

2.4.1. Subacute Herpetic Neuralgia

The use of MeCbl markedly decreased unremitting pain, paroxysmal pain, and allodynia in the subacute herpetic neuralgia (SHN) patients (37) (Table 3). Therefore, Vitamin B12 can be used as an adjuvant treatment for SHN.

2.4.2. Glossopharyngeal Neuralgia

In pain clinics, Glossopharyngeal neuralgia (GPN) is common. It was stated that the numerical pain scales were reduced markedly with the treatment of MeCbl combined with gabapentin and tramadol in GPN patients (38) (Table 3). In addition, the quality of life improved markedly (38).

2.4.3. Trigeminal Neuralgia

The pain of trigeminal neuralgia (TN) can be portrayed as excruciating, paroxysmal and lancinating which may be activated by minor deeds such as chewing, speaking, and swallowing. A recent study showed that the pain of TN patients was eased significantly in the MeCbl group, and no recurrence of TN in 64% of the cases (39) (Table 3).

3. Analgesic Properties

Since many decades, the B12 group of vitamins had been used to treat pain. In some countries, vitamin B12 was labeled as an analgesic drug. It was implied that vitamin B12 may augment the availability and effectiveness of noradrenaline and 5-hydroxytryptamine in the descending inhibitory nociceptive system (40). MeCbl has therapeutic effects on neuropathic pain in diabetics, conceivably through its neurosynthesis and neuroprotective actions (14, 41). However, the analgesic mechanisms of MeCbl continue to be obscure. There are three sets of speculation on that matter below.

3.1. Improving Nerve Conduction Velocity

Several authors revealed that high doses of MeCbl amended nerve conduction in either patients with diabetic neuropathy (13-15), streptozotocin-diabetic rats (16), or experimental acrylamide neuropathy (17). Morphological and histological evidence established that a long-term administration of MeCbl stimulated the synthesis and regeneration of myelin (42). These morphological and histological recoveries of myelin can lead to ameliorating nerve conduction velocity and neuronal function in peripheral neuropathy.

3.2. Promoting the Regeneration of Injured Nerves

In vivo MeCbl advanced the incorporation of radioactive leucine into the protein fraction of the crushed sciatic nerve. Therefore, this led to the recovery of the injured nerve activity (43). In this study, most terminals were degenerated in the mutant mouse, but the sprouts were more often observed in the MeCbl treatment group (44). MeCbl had the power to support the injured nerves' regeneration. In the experimental acrylamide neuropathy and sciatic nerve injury models, the number of regenerations of motor fibers showed significant increase with high-dose methylcobalamin (17). In addition, the combined use of L-methylfolate, MeCbl, and pyridoxal 5'-phosphate ameliorated the calf muscle surface neural density (45).

3.3. Inhibiting Ectopic Spontaneous Discharge

Ectopic spontaneous discharges are possible to start spontaneous pain, hyperalgesia, and allodynia (46-49). It was reported that MeCbl suppressed the ectopic firing triggered by chemical materials in the dog dorsal root (50).

4. Discussion

Chronic pain is a usual complaint, leading the sufferer to be up to five times more likely to pursue medical attention as compared to those people without chronic pain (8). Lumbago, is a main cause of chronic pain. Within a year period one third of patients with this pain will experience lumbago (28). It has also been projected that around 80% of people will have low back pain at some point during their life (27). The bulk of low back pain (90%) without related neurological symptoms improves within 3 months (51). The remaining 10% are a challenge to many healthcare providers, not only because chronic low back pain is challenging to manage, it is also normally linked to anxiety, depression, job dissatisfaction, poor body image and somatization (28)

The therapeutic options for low back pain include NSAIDs, tramadol acetaminophen combinations, non-SSRI antidepressants, and glucocorticoids or local anesthetic to the spine (52). These medications may lead to serious side effects, particularly when used for long periods of time. NSAIDs, for example can lead to kidney dysfunction, acetaminophen can cause liver dysfunction and glucocorticoids can cause weight gain, insomnia, and Cushing syndrome. Studies revealed that out of the available treatments only NSAIDs seem to ameliorate function (52). Recent studies (31,32,33) have shown that injectable cobalamin might also be a promising treatment option for lumbago.

Several studies (53-59), have suggested that large doses of vitamin B12 in combination with NSAIDs may lead to heightening effect on the analgesic properties of NSAIDs, therefore possibly decreasing NSAID dosing.

Vitamin B12 is mostly used for treatment of deficiency, which is often due to malabsorption, insufficient dietary intake, pernicious anemia, gastric surgery, GI disease, and particular medications (60). If longterm effects of vitamin B12 injection show to be safe, vitamin B12 might be a precious treatment alternative for low back pain. This will be particularly important for the elderly, for patients prone to liver or kidney disease or people interested in natural substance. The three randomized clinical trials (31-33) revealed that vitamin B12 compared to placebo, decreases low back pain and improves function significantly. However these studies have limitations, including small size that leads to large confidence intervals that the possibility that treatment effect was not precise. In addition none of the studies investigated the longterm effects of injectable vitamin B12.

It is known that high serum levels of vitamin B12 are linked to cancer, liver, renal, and inflammatory diseases (61). In one study vitamin B12 serum levels of >1275 pg/mL were associated with hematologic malignancies (62). Therefore, it is important to consider the possible side effects associated with long term risk. Studies that evaluate longterm effects of high serum cobalamin levels had their limitations. In one study the age of the patient was important in determining the level of vitamin B12 where the older patients had a higher level (63).

It is known that elderly have multiple comorbidities. Hence it was challenging to attribute the results of the study to the vitamin B12 levels versus the participants age (64). One more limitation is the fact that vitamin B12 was the only lab value looked at for its possible relation to cancer development (65). Other electrolyte abnormality or vitamin deficiency may be implicated for the cause for an increased risk of cancer.

In addition we are not sure that the cobalamin doses used in the treatment of low back pain were high enough to lead to high serum vitamin B12 levels discussed (63,64).

Although vitamin B12 seems to have significant benefit in the treatment of chronic low back pain, further research, with elimination of some of these limiting factors, is needed to study whether the intramuscular vitamin B12 injection doses are indeed harmful in the long run.

5. Conclusions

Intramuscular vitamin B12 injections seem to be effective at ameliorating nonspecific chronic low back pain as compared to placebo. Vitamin B12 injections also have exhibited only minimal side effects, which include hematoma and pain at the injection site.

There is a need for larger study with longer duration that spans several years to assess the longterm side effects. Especially that longterm effects can be possibly serious. Meanwhile, physicians may use vitamin B12 treatments in addition to established treatment to prudently selected patients.

MeCbl or its joint use with other agents has the conceivable analgesic effect in specific patients and animal models, for example, nonspecific low back pain; neck pain; diabetic neuropathic pain, subacute herpetic neuralgia, glossopharyngeal neuralgia, and trigeminal neuralgia. However, the mechanisms underlying the analgesic effect were badly comprehended. On the basis of recent work, the likely mechanisms can be considered as follows. (1) MeCbl improved nerve conduction velocity; (2) MeCbl promoted injured nerve regeneration, recovering the neuromuscular functions in peripheral hyperalgesia and allodynia; and (3) MeCbl inhibited the ectopic spontaneous discharges from peripheral primary sensory neurons in neuropathic pain states. Therefore, MeCbl can be used for treating peripheral neuropathy with good safety.

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