Effectiveness of Vitamin B12 on Diabetic Neuropathy: Systematic Review of Clinical Controlled Trials

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Abstract- The clinical effectiveness of vitamin B12 and its active coenzyme form on diabetic neuropathy is uncertain. Therefore, we searched the English- and non-English-language literature on this topic by using MEDLINE (Ovid, PubMed), the Cochrane Controlled Trials Register, and related papers. We identified seven randomized controlled trials from June 1954 to July 2004 and reviewed them for the clinical effectiveness of vitamin B12 according to the following parameters: Measurement scales of somatic and autonomic symptoms or signs; vibrometer-detected thresholds of vibration perception; and, electrophysiologic measures such as nerve conduction velocities and evoked potentials. Three studies involved the use of vitamin B complex (including B12) as the active drug, and four used methylcobalamin. Two studies were of fairly good quality (Jadad score = 3/5), and five were of poor quality (Jadad score ≤ 2/5). Both the vitamin B12 combination and pure methylcobalamin had beneficial effects on somatic symptoms, such as pain and paresthesia. In three studies, methylcobalamin therapy improved autonomic symptoms. Effects on vibration perception and electrophysiological measures were not consistent. With both the vitamin B12 combination and pure methylcobalamin, symptomatic relief was greater than changes in electrophysiological results. However, more high-quality, double-blind randomized controlled trials are needed to confirm the effects of vitamin B12 on diabetic neuropathy.

Key Words: Systematic review, Randomized controlled trial, Vitamin B12, Methylcobalamin, Diabetic neuropathy

Acta Neurol Taiwan 2005;14:48-54

INTRODUCTION

In 40-50% of people with diabetes mellitus type 1 or type 2, detectable peripheral neuropathy develops within 10 years of the onset of disease, and the neuropathic pain associated with symptomatic disease is frequently bothersome[1,2]. Foot ulceration, which depends on the degree of foot insensitivity[3], and amputation are important and costly sequelae of diabetic neuropathy[4]. Autonomic dysfunction has also been reported as a common complication in patients with diabetes[5,6] and can lead to sexual dysfunction and postural hypotension.

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Received December 8, 2004. Revised December 29, 2004. Accepted February 14, 2005.

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This autonomic dysfunction is difficult to treat and only partially responsive to current therapy.

Vitamin B12 plays a vital role in the metabolism of fatty acids essential for the maintenance of nerve myelin. Prolonged B12 deficiency can lead to nerve degeneration and irreversible neurological damage[7]. Diabetic neuropathy, with or without B12 deficiency, had been treated with neurotropic vitamins for decades. In routine clinical practice, formulations that can be taken orally are usually used. Vitamin B12 is available in three forms: cyanocobalamin, hydrocobalamin, and methylcobalamin. The first is the most widely available and least expensive, but some experts prefer the other two forms.

The treatment of diabetic neuropathy can be a frustrating experience for both physicians and patients, and the clinical effectiveness of vitamin B12 therapy on diabetic peripheral neuropathy is still unclear. The purpose of this review was to investigate and evaluate the reported effectiveness of vitamin B12 supplements to provide evidence-based recommendations for clinical practice.

METHODS

Search strategy

We conducted a systematic review of English- and non-English-language articles using MEDLINE (Ovid, PubMed), the Cochrane Controlled Trials Register, and related papers from June 1954 to July 2004. Additional references were identified by searching bibliographies or related publications. Studies reported in abstracts or conference presentations were excluded from the review because they inadequately reported their methodologies and results and because they had not undergone peer review. We used three main Medical Subject Headings: (1) Trials: randomized controlled trial or controlled-clinical trial or double-blind method or clinical trial; (2) Vitamin B12: methylcobalamin, cyanocobalamin or hydroxycobalamin; (3) Neuropathy: diabetic polyneuropathy, diabetic peripheral neuropathy.

Eligible studies

We included reports if they described randomized controlled trials (RCTs) of any type of vitamin B12 therapy in patients with diabetes peripheral neuropathy. We also included studies of the coenzyme forms of B12, such as methylcobalamin, cyanocobalamin, or hydroxycobalamin in either the oral or injection form. Trials involving combination therapy were eligible only if vitamin B12 or its coenzyme form was one of the treatment agents. Diabetic neuropathy was defined as peripheral large- or small-fiber neuropathy resulting in autonomic or somatic sensory symptoms.

Our primary outcome measure was the clinical effectiveness, as assessed by using three main parameters: 1) Clinical scores of somatic and autonomic symptoms or signs; 2) Vibrometer-detected thresholds of vibration perception; and, 3) Electrophysiological measures such as nerve conduction velocities (NCVs) and somatosensory evoked potentials. We excluded uncontrolled trials, observational studies, animal experiments, and studies focusing on only a specific population such as patients with uremia. Studies of vitamins used for other purposes (eg, encephalopathy, dementia, anemia) were also excluded.

Quality assessment

We assessed the following methodological features that were most relevant to the control of bias by following the guidelines of Jadad scoring system: Randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals[8,9]. Two reviewers independently applied the inclusion criteria. One of them extracted the data and assessed its quality; and the other reviewer checked these results, and any noted differences were resolved by consensus.

Information gathered

To compare clinical effectiveness across studies, consistent information was selected whenever possible. We gathered the following information: Number of patients examined, intervention with monotherapy or a combination regimen, study design, duration of study and follow-up, and outcome measures and results. Clinical effectiveness was assessed by means of a narrative comparison of the different outcomes, which included the mean change or proportion of patients whose

results changed from baseline, mean clinical scores, and mean differences between control and active agents.

RESULTS

Quantity and quality of studies

We identified seven clinical controlled trials that met our inclusion criteria (Fig.)[10-16]. All studies were published in English, except 1, which was published in Chinese. Three studies used vitamin B complex (B1, B6, and B12) as a combination agent[10-12], whereas the other four used pure methylcobalamin as the main treatment[13-16]. In the studies of vitamin B complex, a synthetic derivative of thiamin, ie, Benfotiamine (B1), and cyanocobalamin (B12) 250 µg were given. One study did not mentioned randomization in its clinical controlled trials. Because the investigators described the study design in detail, with no differences between the study groups, we included this study in our review. Although six studies mentioned randomization, all lacked an adequate description, notably how the randomization was generated. None of the studies included an intent-to-treat analysis. Table 1 shows the quality assessments of the studies. Only two studies involved a double-blind process and were judged of fairly good quality (Jadad score = 3/5)[12,15]. The other five studies were of poor quality (Jadad score ≤ 2/5)[10,11,13,14,16].

Table 2 shows the characteristics of the studies. The mean ages of the patients enrolled were all around 50-60

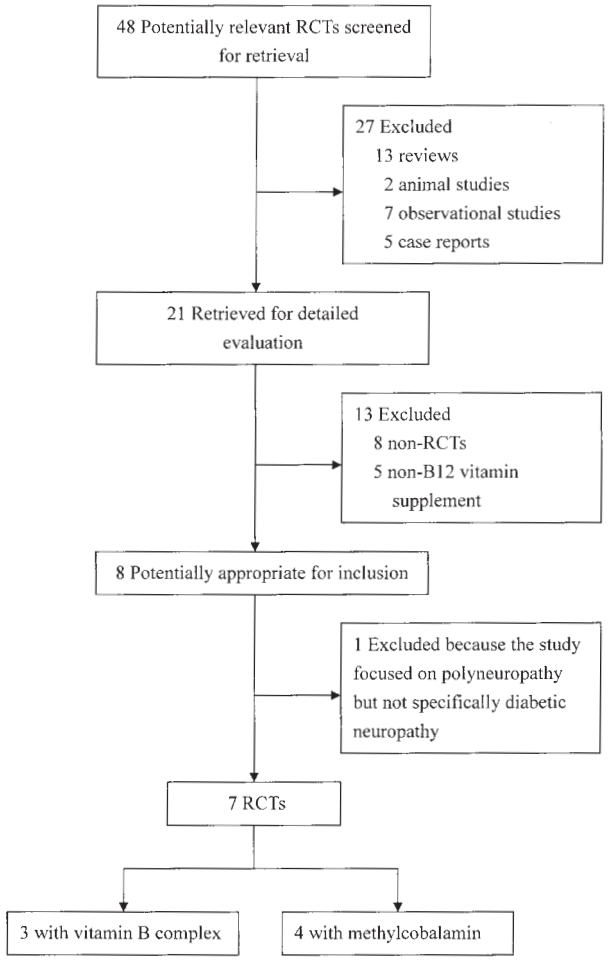

Figure. Flow diagram shows how we identified RCTs that met our criteria.

Table 1. *Quality assessments of included RCTs of vitamin B12 therapy for diabetic neuropathy*

Intervention and study	Randomization*	Double blinding	Effective blinding‡	Intent-to-treat analysis	Dropout rate (%)	Jadad score §
Vitamin B_{12} complex						
Winkler et al[10]	Yes	No	No	No	0	1
Simeonov et al[11]	Yes	No	No	No	0	1
Stracke et al[12]	Yes	Yes	Yes	No	0	3
Methylcobalamin						
Li[13]	Yes	No	No	No	0	1
Shindo et al[14]	No†	No	No	No	0	0
Yaqub et al[15]	Yes	Yes	Yes	No	14	3
Devathasan et al[16]	Yes	No	No	No	12	1

*None of the studies described how the randomization was generated; †Patient characteristics of the study and control groups did not differ significantly; ‡Masking of treatment and matching placebo; §Main items of Jadad scores are as follows: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals.

Table 2. *Characteristics of included studies of vitamin B12 therapy for diabetic neuropathy*

Intervention and study	Patient age (y)	Inclusion criteria	Disease duration (y)	Duration of neuropathic symptoms (y)	Intervention*	Study duration (wk)
Vitamin B_{12} complex						
Winkler et al[10]	56 ± 8	DM type 1 or 2, neuropathic symptoms > 1 y; DM controlled (HbA1c < 8)	NA	NA	Milgamma N 2 tablets qid (n=12); Milgamma N 1 tid (n=12); Benfotiamine 1 tid (n=12)	6
Simeonov et al[11]	56	DM type 1 or 2, peripheral neuropathy	NA	11 (3-18)	Active: Benfotiamine (B1) 50 mg + cyanocobalamin 250 µg 2 qid for 21 d then 1 tid (n=30); control: Neurobex 1 bid (n=15)	12
Stracke et al[12]	59	DM type 1 or 2; age 40-60 y; neuropathic symptoms 4 mo to 3 y	Active: 10; control: 12	NA	Active: Benfotiamine 40 mg + vitamin B6 90 mg + cyanocobalamin 250 µg 2 qid for 14 d then 1 tid (n=11); control: placebo (n=13)	12
Methylcobalamin						
Li[13]	56 ± 1	DM type 2, peripheral neuropathy	Active: 9; control: 8	Active: 3, control 3	Active: Methycobal injection 500 µg injection 3 times per wk for 4 wk then oral form 500 µg tid for 8 wk (n=62); control: vitamin B12 injection 500 µg for 4 wk then oral form 1 tid for 8 wk (n=46)	12
Shindo et al[14]	56 ± 3	DM type 2, peripheral neuropathy	Dietary control: 12; methylcobalamin: 9; PGE: 10	Dietary control: 1; methylcobalamin: 1; PGE: 2	Dietary control (n=13), oral methylcobalamin 500 µg tid (n=13), PGE 1.2 µg/kg/d (n=12)	4
Yaqub et al[15]	56	DM type 1 or 2, peripheral neuropathy, blood sugar controlled (HbA1c 5.5-8%)	9 (5-20)	NA	Active: methylcobalamin 500 mg tid (n=21); control: placebo (n=22)	16
Devathasan et al[16]	53	DM type 1 or 2 diabetes, peripheral neuropathy, DM > 2 y with blood sugar controlled	12	NA	Active: methylcobalamin 500 mg tid (n=21); control: placebo (n=21)	12

DM indicates diabetes mellitus; NA: not available; PGE: prostaglandin E1. Data are the mean ± standard deviation, mean, or mean (range), unless otherwise noted. *Milgamma N is benfotiamine 40 mg + vitamin B6 90 mg + cyanocobalamin 250 µg; Neurobex, 100 mg thiamin + vitamin B6 20 mg + vitamin B12 100 µg (form of B12 not mentioned).

Table 3. *Clinical effectiveness of vitamin B6 therapy for diabetic neuropathy*

Studies	Pain or somatosensory symptoms	Vibration perception	Autonomic symptoms	Electrophysiological measures
Winkler et al[10]	Improved in all 3 groups vs baseline (p<0.01), no difference between groups (modified McGill visual-analogue scales)	Improved in all 3 groups vs baseline (p<0.01), no difference between groups (Riedel and Seyfer calibrated tuning fork)	Not applicable	Current perception improved in all 3 groups vs baseline, most Milgamma N (by neurometer) significant with high-dose
Simeonov et al[11]	Improve in both groups vs baseline (p<0.001); bentothiamin with cyanocobalamin complex better than Neurobex (p<0.001; 0-20 graphic rating scale)	Improved in both groups vs baseline (p<0.01; Riedel and Seyfer biothesiometer)	Not applicable	Not applicable
Stracke et al[12]	Not applicable	Improved vs placebo (Somedic vibrometer, model type III; Stockholm, Sweden)	Not applicable	Improved vs placebo (p=0.006 (by NCV study in the peroneal and median nerves)
Li[13]	Methycobal better than control in pain, numbness, and thermosensation (p<0.05; 4-point scale)	Not applicable	Methycobal better than control in oral dryness and dysuria (4-point scale)	NCVs improved in peroneal nerve vs control (p=0.033)
Shindo et al[14]	Improvement rates: dietarycontrol, 20%; methylcobalamin, 50%; PGE, 100% (4-point scale)	No improvement with methylcobalamin or diet control (vibrometer, SMV-5)	Not applicable	Not applicable
Yaqub et al[15]	Improve in active group (p=0.003; peripheral neurophysiology score)	Not applicable	Improved in active group (p=0.01; peripheral neurophysiology score)	No change in motor score; sensory score improved but no statistically significant (by NCV study)
Devathasan et al[16]	Improve in active group (p<0.01; 4-point scale)	Not applicable	Improved in active group (p<0.01; 4-point scale)	NCV improved in active group in median and sural nerves (p<0.05 for median nerve SSEP; p=0.05 for MNCV/H reflex/SSEP on median, tibial, popliteal, and sural nerves)

MNCV indicates motor nerve conduction velocity; Neurobex: 100 mg thiamin + vitamin B6 20 mg + vitamin B12 100 μg ; PGE: prostaglandin E1; SMV-5: Suzuki-Matsuoka vibrometer; SSEP: somatosensory evoked potential.

years. Two studies of methylcobalamin included only patients with diabetes type 2[13,14]. Patients with vitamin B12 deficiency were excluded in only one study[12]. In most of the studies, the mean duration of diabetes mellitus was 9-12 years. The patients in one study had long-term neuropathic symptoms[11]. Vitamin B complex, including vitamin B1, B6, and B12, was the interventional agent in three studies[10-12]. In one study, the injected form of methylcobalamin was given in the active group, followed by the oral form; however, the study

report did not describe which form of B12 was injected in the control group[13]. Three other studies used the oral form of pure methylcobalamin as the main treatment[14-16]. The duration of intervention in all included studies ranged from 4 to 16 weeks.

Clinical effectiveness

Overall, the measuring parameters or scoring systems differed between studies; therefore, a meta-analysis was hard to do. Of the six trials[10,11,13-16] in which pain or somatosensory symptoms were measured, all involved different scoring scales and all showed a statistically significant beneficial outcome with vitamin B complex or methylcobalamin treatment compared with baseline or placebo results (Table 3). Of the four trials in which the vibration perception threshold was tested, 3[10-12] showed a beneficial outcome and 1[14] did not show a significant improvement with methylcobalamin treatment. Methylcobalamin improved autonomic symptoms in three studies[13,15,16]. As for assessment of peripheral nerve function from electrophysiological studies, one study used a neuromotor assessment process to measure the current perception threshold and demonstrated a beneficial outcome with vitamin B complex. Of the trials that included testing of NCVs, one study of vitamin B combination therapy and one study of methylcobalamin revealed beneficial outcomes[12,16] compared with placebo. In one study, outcomes were better with methylcobalamin than with conventional vitamin B12 (though the form of B12 was not described clearly) in terms of autonomic symptoms, somatosensory symptoms, and electrophysiological results[13]. However, one double-blinded placebo-controlled trial showed no change or significant improvement on NCV with methylcobalamin compared with placebo[15].

DISCUSSION

We conducted this systematic review to explore the efficacy of vitamin B12 therapy on diabetic neuropathy in limited RCTs and also to assess the quality of the included studies. A clinical trial of this treatment regimen was published as early as 1954[17]. It was an observational study without randomization or a matched placebo or blinding process. Although diabetic neuropathy has been treated with neurotropic vitamins for decades, high-quality RCTs of this intervention are still lacking. Most RCTs have not used a double-blind design; this is a problem because selection bias cannot be reduced without adequate randomization and use of blind controls[8]. Furthermore, the small number of participants in most RCTs may reduce the validity of the findings.

Other problems in this review were the variability of the intervention (which included multicomponent vitamin B, the injected form of methylcobaloamin, or the oral form of methylcobalamin) and the diverse scoring systems used in measuring outcomes. Therefore, quantitative pooling of the data was not feasible for our analysis of the results. Instead, we individually summarized the efficacies of viamin B12 acording to four main items: Pain and somatosensory symptoms, autonomic symptoms, vibration perception, and electrophysiologic measures (mainly NCV). Our results showed that treatment with either vitamin B complex or pure methylcobalamin had beneficial effects on somatosensory symptoms, such as pain and paresthesia, though two RCTs of the vitamin complex with cyanocobalamin did not involve a double-blind design. Those latter RCT's may therefore have resulted in overestimation of the treatment effects[8]. As for methylcobalamin therapy, its benefits on autonomic symptoms (improved in three studies) were as consistent as its effects on pain and somatosensory symptoms (improved in all four studies), and they were relatively reliable, as shown in one placebo-controlled trial with a double-blind design. Vitamin B complex treatment slightly improved the vibration perception threshold, whereas methylcobalamin provided no benefit. Improvement in neurophysiological parameters was not as evident as changes in clinical signs and symptoms. A possible explanation could be that the duration of treatment was not long enough for the long fibers to regenerate.

Some investigators have reported that antidiabetes drugs, such as metformin, may induce B12 deficiency[18]. Therefore, vitamin B12 or methylcobalamin treatment

may correct this deficiency state and possibly convert its related neuropathy. This mechanism might explain its inconsistent effects in the treatment of diabetic neuropathy. In our review, only one RCT excluded subjects with vitamin B12 deficiency. Future subgroup analysis of diabetic participants with or without B12 deficiency in clinical trials of vitamin therapy is important.

In conclusion, treatment with both combination agents (vitamin B complex with cyanocobalamin) and pure methylcobalamin appeared to improve symptomatic relief more than electrophysiologic results among patients with diabetic neuropathy. However, more high-quality, double-blind RCTs are needed to confirm the clinical effectiveness of vitamin B12 and its active coenzyme.

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