The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial

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ABSTRACT

Introduction: Chronic, nonspecific low back pain is a difficult ailment to treat and poses an economic burden in terms of medical expenses and productivity loss. The aim of this study was to determine the efficacy and safety of intramuscular metylcobalamin in the treatment of chronic nonspecific low back pain.

Methods: This was a double-blinded, randomised, controlled experimental study. 60 patients were assigned to either the methylcobalamin group or the placebo group. The former received intramuscular injections of 500 mcg parenteral methylcobalamin in 1 ml solution three times a week for two weeks, and the placebo group received 1 ml normal saline. Patients were assessed with Oswestry Disability Index questionnaire Version 2.0 and Visual Analogue Scale pain score. They were scored before commencement of the injections and at two months interval.

Results: Of the 60 patients, 27 received the placebo injections and 33 were given methylcobalamin injections. A total of 58 patients were available for review at two months (placebo: n is 26; methylcobalamin: n is 32). There was a significant improvement in the Oswestry Disability Index and Visual Analogue Scale pain scores in the methylcobalamin group as compared with the placebo group (p-value less than 0.05). Only minor adverse reactions such as pain and haematoma at the injection sites were reported by some patients.

Conclusion: Intramuscular methylcobalamin is both an effective and safe method of treatment for patients with nonspecific low back pain, both singly or in combination with other forms of treatment.

Keywords: methylcobalamin, nonspecific low back pain, vitamin B_{12}

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INTRODUCTION

Low back pain (LBP) affects a substantial proportion of the population. Almost every person will encounter an episode of back pain at some point in one's life. Back pain does not discriminate based on gender, age, race or culture. It disables the working adult from performing his duties and paralyses the society due to the cost incurred in terms of treatment and productivity loss. In 1988, a survey was conducted in a semirural area in Malaysia. A total of 2,594 individuals from a multi-racial (Malay, Chinese, Indian) community were interviewed. The Community Orientated Programme for the Control of Rheumatic Diseases protocol was utilised. The survey reported that up to 11.6% of the population were affected by LBP.[1]

Nonspecific low back pain (NSLBP) refers to pain that cannot be fully explained and has no apparent physical cause. There is no causal link between any specific physical diagnosis and the pain. NSLBP can be defined by symptoms occurring primarily in the back, which suggests neither nerve root compression nor a serious underlying condition. There is no verifiable physical pathology, anatomic lesion or deformity identified that can link to the patient's symptoms. NSLBP encompasses common diagnoses such as lumbago, myofascial syndromes, muscle spasms, mechanical LBP, back sprain and strain. Patients with these vague conditions have pain in the lumbar region that may radiate to one or both thighs. The published literature reports that up to 85% of patients aged 25–55 years with back pain were diagnosed with NSLBP.[2,3]

The use of vitamin B_{12} in the treatment of LBP has been established. In animal studies, vitamin B_{12} has been shown

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to reduce pain in the test subjects.[4-9] Its synergistic effect with non-steroidal anti-inflammatory drugs (NSAIDs) has also been proven in laboratory animal tests.[10-13] In clinical setting, vitamin B_{12} was found to reduce NSAID dosage and its duration in patients with back pain.[14-16] Methylcobalamin, an active analogue of vitamin B_{12}, has been shown to improve neuropathic pain[17-19] and neurologic claudication distance in patients with lumbar spinal stenosis.[20] Some postulate that vitamin B_{12} has analgesic properties or analgesia-enhancing actions that increase the availability and effectiveness of noradrenaline and 5-hydroxytryptamine, acting as inhibitory transmitters in the nociceptive system.[21] However, these properties were only noted when high concentrations of the vitamin were administered. There were others who claimed that no strong evidence exists to prove that B vitamins have any analgesic properties.[22-24] Intramuscular administration of vitamin B_{12} is known to produce rapid and higher serum levels.[25,26] It is hypothesised that a higher level of serum vitamin B_{12} is needed to ensure the exhibition of the nociceptive therapeutic action.

To date, only one prospective study in Europe had looked into the effectiveness of intramuscular vitamin B_{12} in alleviating LBP and its related disability. In this double-blinded, randomised clinical trial, intramuscular Tricortin 1000 (1000 μg Vitamin B_{12} in 2-ml ampoules) was used, and the authors concluded that parenteral vitamin B_{12} is efficacious and safe in treating patients with LBP.[27] The current study was conducted to determine the actual role of vitamin B_{12} in the management of chronic NSLBP.

METHODS

This was a double-blinded, randomised controlled experimental study in which randomisation was done with a computerised software. The study was approved by the medical ethics board and registered under the Malaysian Science and Technology Information Centre. Patients of both genders, aged 20–65 years with symptoms of NSLBP lasting more than six months and who fulfilled the inclusion and exclusion criteria, were randomly assigned to one of the two study groups. The treatment group received methylcobal containing 500 μg of parenteral methylcobalamin in 1-ml ampoules, and the placebo group received normal saline. The study was conducted at the Orthopaedic Specialist Clinic of Hospital Tuanku Jaafar, Malaysia from August 2006 to April 2007. The sample size was determined based on an estimation to achieve a study power of 80% and a 5% level of significance. The two main research instruments used were the Oswestry Disability Index (ODI) questionnaire Version 2.0 and Visual Analogue Scale (VAS) pain score.

Before the initiation of treatment, the patients were instructed to complete the ODI questionnaires and to chart their VAS pain scores. A total of six intramuscular injections of methylcobal were administered to the patients in two weeks (three intramuscular injections were given on Days 1, 3 and 5 each week). This regime was the recommended dosage for peripheral neuropathy. All patients were also prescribed tablet paracetamol and advised to consume when needed, with a maximal dose of 3 g per day. The patients were followed up for two months after the initiation of treatment, and the ODI questionnaires and VAS pain scores were taken at the end of the period.

Pregnant women, patients on drugs known to have toxic effects on peripheral nerves, those with severe concurrent illnesses (e.g. uncontrolled diabetes mellitus or hypertension, ischaemic heart disease, end-stage renal failure, cerebral vascular disease or malignant cancers), known B_{12} allergy, megaloblastic anaemia, symptoms suggestive of specific LBP (including symptoms that can be attributed to a systemic disease, infection, tumour, injury, trauma or structural deformity) and patients who wished to continue with other forms of treatment (e.g NSAIDs, physiotherapy or exercise programmes) were excluded from the study. In addition, the patients were informed that they could withdraw from the study at any time, without any prior notice and without any consequences. They would still be able to receive all other forms of appropriate treatments from the hospital without any bias or prejudice.

RESULTS

A total of 60 patients were included in the study, of which 45% were male. The average age of the sample population was 47.6 ± 9.6 (range 30–65) years. The average body mass index (BMI) was 24.9 ± 2.9 kg/m^2, with female subjects having slightly higher BMIs than the male subjects (25.8 ± 3.0 kg/m^2). The placebo group consisted of 27 patients and the methylcoblamin group, 33 patients. There was no significant difference between the two groups in terms of gender, age, BMI, ODI scores and VAS scores ($p > 0.05$), which indicates that the sample population from the two groups was homogenous.

At two months, 58 patients were available for review, with 26 from the placebo group and 32 from the methylcobalamin group. Two patients voluntarily withdrew from the study (one patient each from the placebo and treatment groups) due to adverse reactions

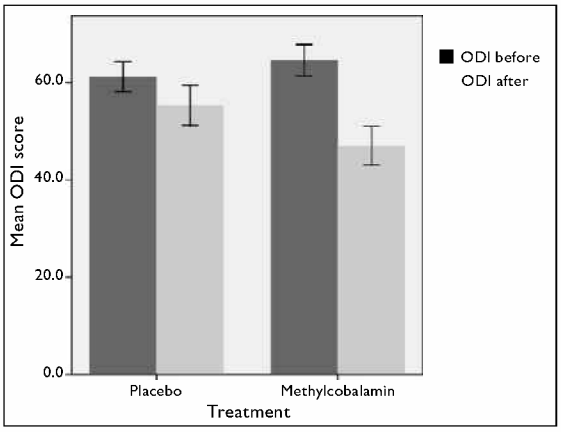

Fig. 1 Graph shows the mean Oswestry Disability Index scores at baseline and post treatment.

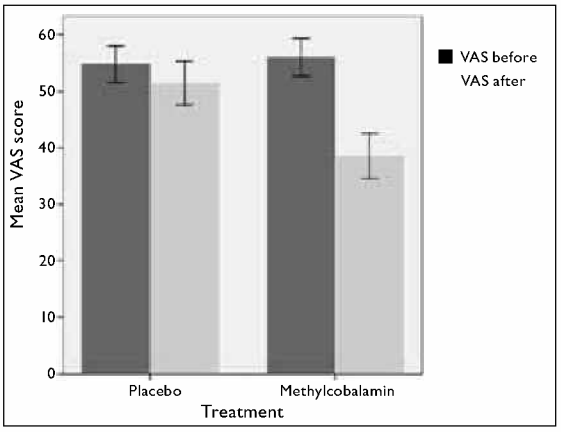

Fig. 2 Graph shows the mean Visual Analogue Scale pain scores at baseline and post treatment.

Table I. Mean Oswestry Disability Index (ODI) scores at baseline and post treatment.

Group	Mean ODI ± SD		p-value*
	Baseline (0 mth)	Post treatment (2 mth)	
Placebo	60.5 ± 15.4	55.3 ± 20.5	0.102
Methylcobalamin	64.0 ± 18.3	47.0 ± 22.3	< 0.001

* Wilcoxon signed-ranks test. SD: standard deviation

Table II. Mean Visual Analogue Scale (VAS) pain scores at baseline and post treatment.

Group	Mean VAS ± SD		p-value*
	Baseline (0 mth)	Post treatment (2 mth)	
Placebo	54.8 ± 16.1	51.5 ± 19.4	0.420
Methylcobalamin	56.0 ± 18.6	38.6 ± 22.3	< 0.001

* Paired *t*-test. SD: standard deviation

(pain and haematoma) and lack of improvement in the symptoms.

No significant reduction in ODI scores was observed in the placebo group ($p > 0.05$) after two months. However, we found a significant reduction in ODI scores in the methylcobalamin group ($p < 0.05$), from 64.0 ± 18.3 to 47.0 ± 22.3, with a mean difference of 17.0 (Table I & Fig. 1). Similarly, no significant reduction in VAS scores was noted in the placebo group ($p > 0.05$) after two months, but we found a significant reduction in VAS scores in the methylcobalamin group ($p < 0.05$), from 56.0 ± 18.6 to 38.6 ± 22.3, with a mean difference of 17.4. (Table II & Fig. 2). The consumption of paracetamol was significantly lower in the methylcobalamin group compared to the placebo group ($p < 0.05$) (Table III and Fig. 3). Approximately 40% of the patients encountered minor adverse reactions, mainly persistent pain (lasting > 24 hours) and haematoma at the injection site (Fig. 4).

DISCUSSION

The results of this study showed that parenteral intramuscular injection of methylcobalamin was more effective than the placebo in relieving NSLBP and its related disability. The value of methylcobalamin in the treatment of NSLBP is based on two postulated fundamental modes of therapeutic action exhibited by it, namely the analgesic and analgesia-potentiating/enhancing properties, as well as its neurosynthesis/neuroprotective properties.

For many years, methylcobalamin and the B_{12} group of vitamins had been used to treat pain. In some countries, vitamin B_{12} is categorised as an analgesic drug. Scientists have been searching for the basis for its pain-relieving and pain-potentiating properties. To this end, numerous animal studies have been conducted to date,[4-8] and all of these studies have shown favourable results, indicating that vitamin B_{12} does indeed possess analgesic characteristics. A few theories concerning the analgesic properties of vitamin B_{12} have been postulated. One such theory suggested that the analgesic effect of vitamin B_{12} is the result of its inhibition of synthesis and action of inflammatory mediators.[7] Another theory attributed the analgesic effect of vitamin B_{12} to an increased availability and effectiveness of noradrenaline and 5-hydroxytryptamine acting as inhibitory transmitters in the nociceptive system.[21]

Vitamin B_{12} is often used in combination with other analgesics, especially NSAIDs. When used in combination, it can potentiate the painkilling effect of NSAIDs, and thus, reduce the dose and shorten the duration needed to achieve the similar analgesic effects of NSAIDs alone. In experimental animal studies conducted on rats, the analgesic properties of vitamin B_{12} were found to have a synergistic effect with NSAIDs.[10-13] Several

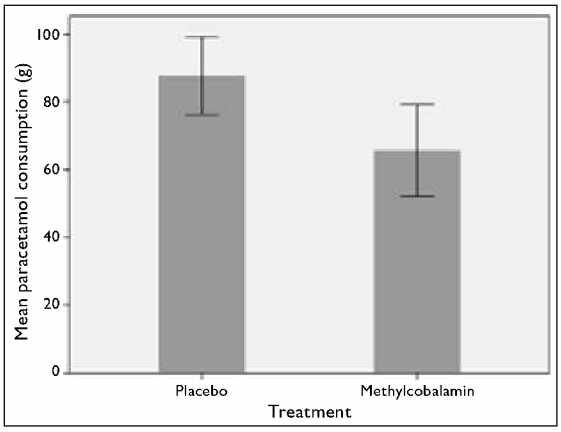

Fig. 3 Graph shows the consumption of paracetamol in the placebo and metylcobalamin groups.

Table III. Paracetamol consumption in the placebo and methylcobalamin groups.

Group	Mean paracetamol ± SD (g)	p-value*
Placebo	87.6 ± 57.3	0.04
Methylcobalamin	65.7 ± 75.2	

* Mann-Whitney test. SD: standard deviation

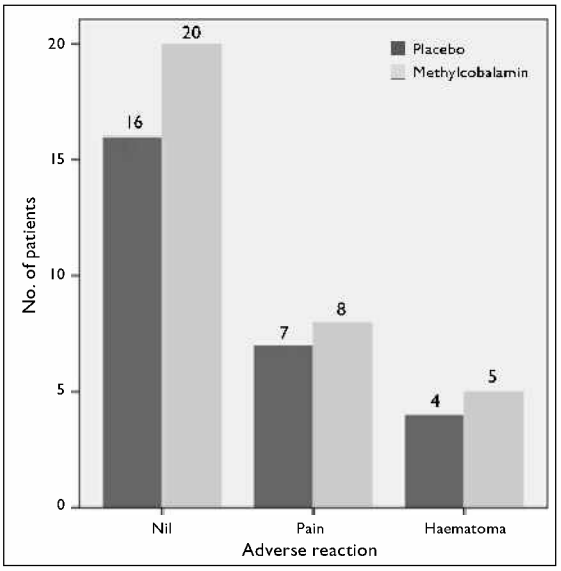

Fig. 4 Graph shows the adverse reactions in the placebo and methylcobalamin groups.

clinical studies examining this analgesia-potentiating property of vitamin B_{12} have found that it has a positive influence in alleviating pain by reducing NSAID dosages and its duration in patients with back pain.[14-16]

Moreover, evidence-based studies have shown that methylcobalamin improves neuropathic pain.[17-19] Peripheral neuropathy, a known complication in patients with diabetes mellitus, frequently causes neuropathic and somatic pain in these patients, which may be due to degradation of the peripheral nerves caused by the disease. Methylcobalamin has been found to improve neuropathic and somatic pain in diabetics, possibly through its neuro-synthesis and neuro-protective actions.[17,18] Waikakul et al found that methylcobalamin improved the neurologic claudication distance in patients with lumbar spinal stenosis in a clinical trial done in 153 patients with a two-year follow-up period.[20]

The question of how the principal function of methylcobalamin is linked to the treatment success of NSLBP has yet to be answered. Even with the distinction in LBP classification into specific and nonspecific, the natural progression of nerve root pain from a non-serious spinal disorder may not present with a specific clinical finding initially. In lumbar disc disease, it has been shown that most patients who were hospitalised for sciatica would have suffered their first episode of LBP while in their third decade of life, with an approximate mean interval of ten years.[28] Weber attributed this long interval between the onset of LBP and the onset of radicular pain to intradiscal degeneration and regeneration forces.[28] The considerable overlap between nerve root compression pain and NSLBP occurs due to the undetectable clinical and radiographic features early in the disease process. A retrospective review of 1,293 patients with a diagnosis of NSLBP over a 12-year period revealed that almost 30% had an identifiable nerve root compression lesion.[29] This points to the proposition that early nerve root irritation may fall under the diagnosis of NSLBP, which may be effectively treated with intramuscular methylcobalamin.

Conservative management is still the mainstay of treatment recommended by practitioners for mild to moderate nerve root compression disease.[30,31] Prospective studies have shown that there was no significant difference in the long-term outcome between surgical and nonsurgical treatment in patients with nerve root compression due to lumbar disc herniation.[28,32,33] Surgery is usually reserved for those with severe or progressive neurological symptoms and for those with intractable pain. In most instances, a multimodal treatment approach, which consists of physical therapy, physical modalities, education and pharmacotherapy, is used. Therefore, we recommend that intramuscular methylcobalamin could be an option in addition to the multimodal treatment of early sciatica.

The full potency of methylcobalamin in relieving pain and potentiating/enhancing analgesia is based on its ability to deliver high doses of the vitamin into the serum. Therefore, a parenteral route was selected over oral medication in order to achieve this effect. Intramuscular administration is preferred to intravenous administration, as it is less invasive but as efficacious as the

intravenous route. Studies have shown that intramuscular administration of methylcobalamin produces rapid and higher therapeutic serum levels in humans.[25,26] Both the placebo and methylcobalamin exhibited only minor adverse reactions, as shown in Fig. 4. These adverse reactions resolved spontaneously without any active treatment. No serious adverse events were recorded throughout the study. Thus, we found that intramuscular methylcobalamin is safe for use in the treatment of patients with NSLBP.

Intramuscular methylcobalamin may prove to be a useful additional treatment for NSLBP, which may include a wide variety of disorders, such as chronic non-neurological intervertebral disorders, degenerative disorders of the spine and musculoskeletal problems of the lower back. However, due to the limitations of this study, only short-term benefits were recorded, and thus, the long-term effects of intramuscular methylcobalamin remain unknown. Further studies to examine the long-term benefits of intramuscular methylcobalamin are required.

In conclusion, intramuscular methylcobalamin is both effective and safe when used to treat patients with NSLBP. Our patients experienced significantly less pain after two months of treatment, required significantly less analgesics, and had improvements in their disability scores. Only mild adverse reactions were observed in some patients. Therefore, intramuscular methylcobalamin is an efficacious medication, used either in isolation or as an adjunct to other forms of treatment, for patients with NSLBP.

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