

Vitamin B₁₂ in low back pain: a randomised, double-blind, placebo-controlled study

G. LETIZIA MAURO, U. MARTORANA, P. CATALDO, G. BRANCATO, G. LETIZIA

Clinica Ortopedica e Traumatologica con Fisioterapia e Medicina dello Sport, University of Palermo - Palermo (Italy)

Abstract. – **Objectives:** The objective of this double-blind randomised, placebo-controlled study was to examine the efficacy and safety intramuscular vitamin B₁₂ (Tricortin 1000) in the treatment of low back pain in patients with mechanical or irritative lumbago.

Methods: 60 patients aged between 18 and 65 years with lumbago or sciatic neuritis of mechanical origin without need for surgical procedures were enrolled. Patients had to present with a proven medical history for back pain (lasting from 6 months to 5 years) and a pain intensity [as evaluated with a Visual Analogic Scale (VAS)] equal or greater than 60 mm. Efficacy primary end-point was evaluated by means of a visual analogic scale (VAS) and a Disability Questionnaire (DQ). Consumption of paracetamol during the study period was the secondary efficacy end-point.

Results: 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 VAS and DQ ($p < 0.0001$ and $p < 0.0002$, respectively). Consumption of paracetamol proved significantly higher in the placebo group than in the active treatment ($p < 0.0001$).

Conclusions: The efficacy and safety of parenteral Vitamin B₁₂ in alleviating low back pain and related disability and in decreasing the consumption of paracetamol was confirmed in patients with no signs of nutritional deficiency.

Key Words:

Vitamin B₁₂, low back pain, paracetamol.

Introduction

Vitamins of the B group are known for their established therapeutical role in neurologic diseases related to a deficiency of these essential nutritional factors. Besides that, therapeutic

benefits of B-vitamins given in high dose, and in particular vitamin B₁₂, in painful disorders of spinal nerve roots in the absence of typical signs of a nutritional deficiency have already been demonstrated. This compound, after conversion into co-enzymatic forms such as methylcobalamin, is involved in the synthesis of nucleic acid and protein, based on the trans-methylation reaction, as well as the metabolism of phospholipids and catecholamines. The methyl group is used in the synthesis of methionine from homocysteine as well as the synthesis of phosphatidylcholine, a phospholipid important in the cell membrane structure. Part of phosphatidylcholine becomes choline and is used in the synthesis of acetylcholine, a notable neurotransmitter.

Animal models demonstrated that B-vitamins yield antinociceptive and antiinflammatory properties in the rat tail pressure test¹, and are able to significantly decrease the responses evoked in spinal dorsal horn nociceptive neurons in the cat².

From a clinical standpoint, several studies have documented the positive influence of B-vitamins of painful symptoms due to degenerative disorders of the lumbar spine, and have indicated that less nonsteroidal antiinflammatory drugs (NSAIDs) are needed for pain relief when combined with B-vitamins^{3,4}. Further investigations conformed the efficacy of Vitamin B₁₂ in the treatment of peripheral neuropathy⁵.

In the present investigation, we have studied the efficacy and safety of intramuscular vitamin B₁₂ (Tricortin® 1000 ampoules)* for the treatment of low back pain in patients with mechanical or irritative lumbago.

*Fidia S.p.A., Via Ponte della Fabbrica, 3a
35031 Abano Terme (PD) - Italy

Patients and Methods

Patients

The study was approved by the Institutional Review Board of the Palermo University Hospital, Palermo, Italy, as special postmarketing surveillance. Patients were given an explanation of the study, and their informed written consent was obtained. All patients were selected from the outpatient clinic of the Department of Orthopaedics of Palermo University Hospital.

Inclusion criteria included subjects aged between 18 and 65 years with lumbago or sciatic neuritis of mechanical origin without need for surgical procedures. Patients had to present with a proven medical history for back pain (lasting from 6 months to 5 years) and a pain intensity [as evaluated with a visual analogic scale (VAS)] equal or greater than 60 mm.

Exclusion criteria included pregnancy, concomitant treatment with drugs known for a toxic effect on the peripheral nerve, severe concurrent illnesses, and intolerance to paracetamol (which was the only allowed NSAID).

The assessors were given no information about treatment assignment.

Patients who met the selection criteria were randomly divided into two treatment groups (active treatment and placebo) of 30 patients each. The mean age \pm SD at the start of the study was 48.8 ± 13.1 years in the active treatment group and 50.4 ± 13.6 in the

placebo group; there was no significant between-group difference (Mann-Whitney *U* test). There were 8 males and 22 females in the active treatment group and 3 males and 27 females in the placebo group; this difference was not significant (Chi-square test). Baseline pain (as evaluated by VAS from 0 to 100 mm), and functional disability (evaluated by a validated disability questionnaire; DQ) were more severe in the active treatment group (Table I).

Methods

Treatments

Both active treatment (Tricortin® 1000 2 mL ampoules containing 1000 mg Vitamin B₁₂) and placebo (2 mL ampoules) were administered once daily by the intramuscular route for a 2-week period.

Efficacy

VAS was evaluated according to *Scott & Huskisson*⁶ by means of a graduated rule with a total length of 100 mm; absence of pain corresponded to the position at 0 mm, and maximum pain to the position at 100 mm.

Functional disability was scored using a validated disability questionnaire (DQ)⁷ consisting of 24 questions, each item corresponding to a single score. Disability could then range from 0 to 24.

Table I. Clinical data of the 2 study groups.

	Tricortin group (n = 30)	Placebo group (n = 30)	P*
Age (y)	48.8 \pm 13.1	50.4 \pm 13.6	0.6443
Sex (n)			
Male	8	3	0.0953 [#]
Female	22	27	
Pain (VAS)	75.5 \pm 8.9	70.6 \pm 7.9	0.0327
Functional Disability (DQ)	13.2 \pm 2.7	11.5 \pm 2.1	0.0105

All values are expressed as mean \pm SD.

*Per Mann-Whitney U test.

[#]Per Chi-square test.

Safety

Safety of treatments was assessed by measuring vital signs (heart rate, diastolic and systolic blood pressure) in each patients in basal conditions and at the end of therapy. The occurrence of adverse events was monitored according to standard pharmacovigilance procedures. If a serious event would have occurred, the breaking of the randomisation code was allowed.

Concurrent drugs

Patients were allowed to take any drugs not related to low back pain, if they needed them, according to their individual clinical condition. Patients needing drugs with a potential toxic effect on the peripheral nervous system were excluded from the study. In both treatment groups, standard doses of paracetamol (1-6 500 mg tablets/day) were given for back pain, if needed. Paracetamol accountability was included as an indirect mean to evaluate treatments (secondary end-point).

Statistical analysis

Sample size was calculated in order to determine a minimum difference between groups of 15 mm at the VAS scale, assuming a standard deviation of 20 mm and a study potency (1-β) equal to 80%.

All statistical tests used were 2-tailed. Within-group comparisons were performed using the Wilcoxon test for paired samples; between-group comparisons were made using the Mann-Whitney *U* test (except for sex distribution, which was analysed with the chi-square test, and paracetamol consumption which was analysed by the unpaired Student *t* test with Welch's correction to account for non-equal variances). Statistical significance was corroborated by analysis of variance and analysis of co-variance tests. The *a priori* level of significance was $\alpha = 0.05$. All analyses were performed using the SAS statistical package (SAS Institute, Cary, NC, USA).

Results

Both treatment groups experienced a sharp decrease in pain and disability. In patients treated with active treatment the pairing was significantly effective ($p = 0.0011$; Spearman's approximation $r_s = 0.5366$) and VAS scale measurement lowered from 75.53 ± 8.9 to 9.53 ± 16.5 mm ($p < 0.0001$); in patients treated with placebo, VAS scores decreased from 70.63 ± 7.9 to 36.83 ± 27.4 ($p < 0.0001$) (Figure 1). However, comparison between

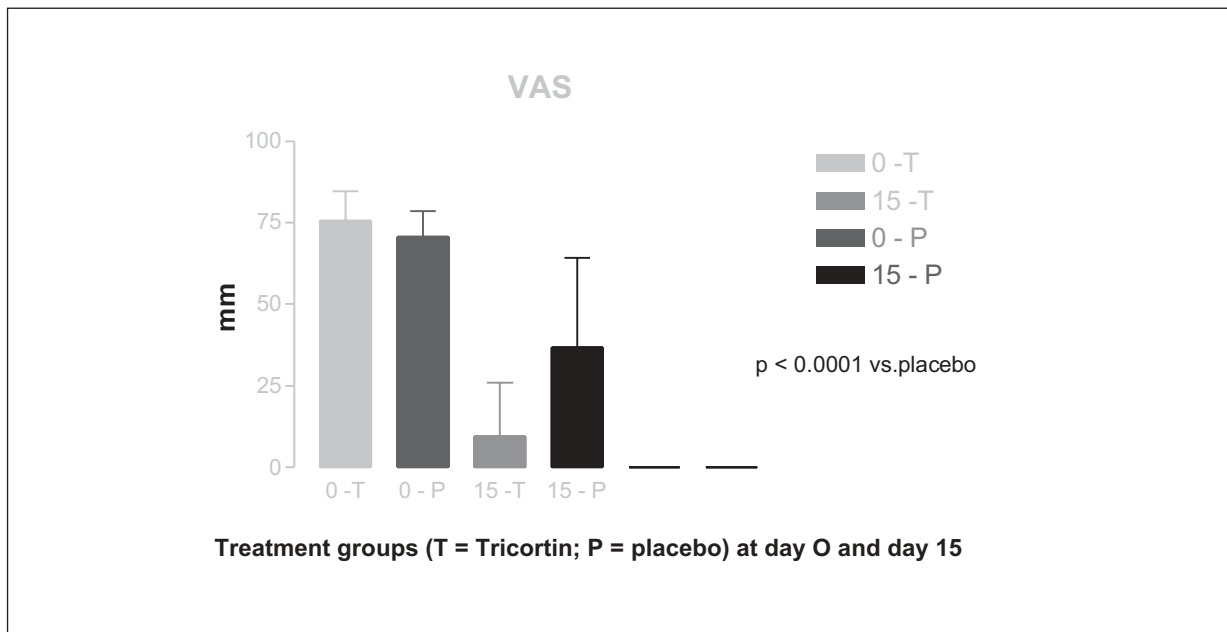


Figure 1.

groups at the end of the treatment period showed a statistically significant difference in favour of the active treatment ($p < 0.0001$).

The analysis of the Disability Questionnaire showed a similar pattern. Total scores declined from 13.27 ± 2.7 to 2.43 ± 2.6 in the active treatment group ($p < 0.0001$) and again paring proved to be effective ($p = 0.0131$; Spearman's approximation $r_s = 0.4057$), and from 11.53 ± 2.2 to 5.80 ± 3.3 in the placebo group ($p < 0.0001$). Between-group comparison at the end of the treatment period demonstrated a significant difference ($p < 0.0002$) in favour of Tricortin (Figure 2).

ANCOVA corroborated these findings.

Mean consumption of paracetamol proved significantly higher in the placebo group than in the active treatment group (28.9 ± 11.32 vs. 9.9 ± 8.04 tablets/15 days; $p < 0.0001$) (Figure 3).

Eight patients in the active treatment group did not take a single paracetamol tablet, vs. only 1 subject in the placebo group. There was no linear correlation between basal VAS values and number of paracetamol tables taken during the treatment period in both groups ($r^2 = 0.0053$ and 0.0014 , respectively). A significant correlation was found between VAS and DQ scores ($r^2 = 0.852$ and $r^2 = 0.845$, respectively; $p < 0.0001$) in both groups. Figure 4 shows the linear regression line for this correlation in the active treatment group.

Safety was excellent in both groups. No changes in vital signs, nor adverse effects were noted.

Discussion

The vertebral pain syndrome is one of the main problem both general practitioners and orthopaedics are confronted with, being as frequent as in 11% of all men and 9.5% of all women in the USA. 63% of all lost working days in people with a physically demanding job are caused by back pain⁸.

In a study conducted in the state of Washington, 321 patients with low back pain persisting for one week were randomized to receive one of three treatments: physical therapy, chiropractic manipulation, or provision of an educational booklet⁹. Most subjects had had back pain for less than 6 weeks. Outcomes at 4- and 52-week time points were similar between the physical therapy and chiropractic groups, and both groups were only marginally better than patients who received the educational booklet only. Patients randomized to the educational booklet were treated at lower cost and tended to be dissatisfied with their care, but there were no differences between the groups in numbers of days of reduced activity, missed work, or re-

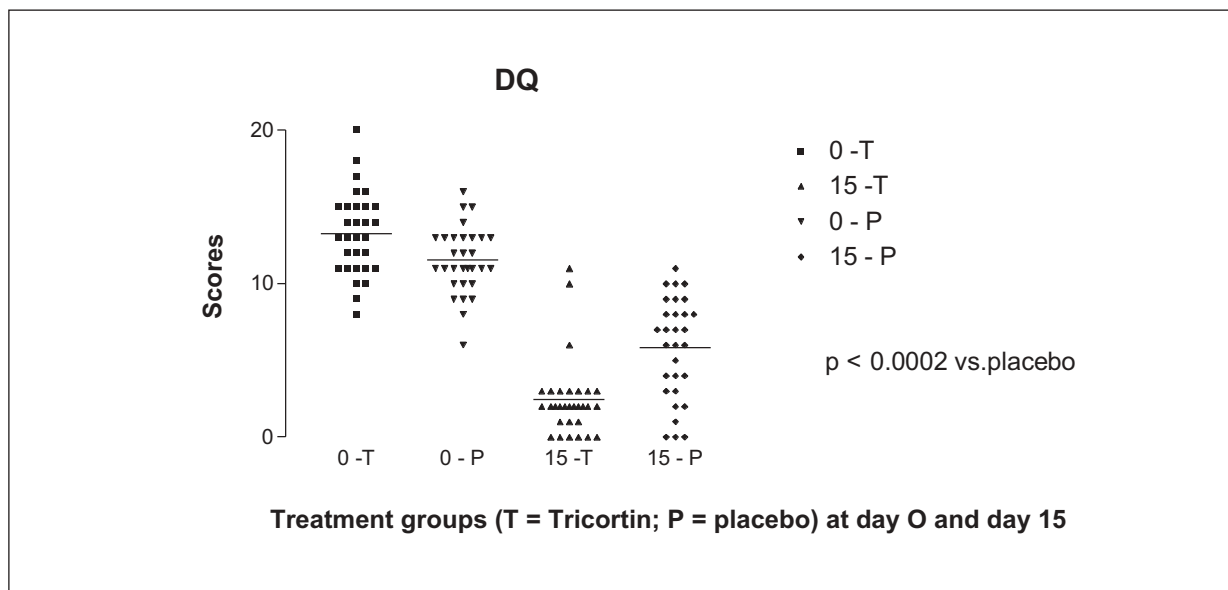


Figure 2.

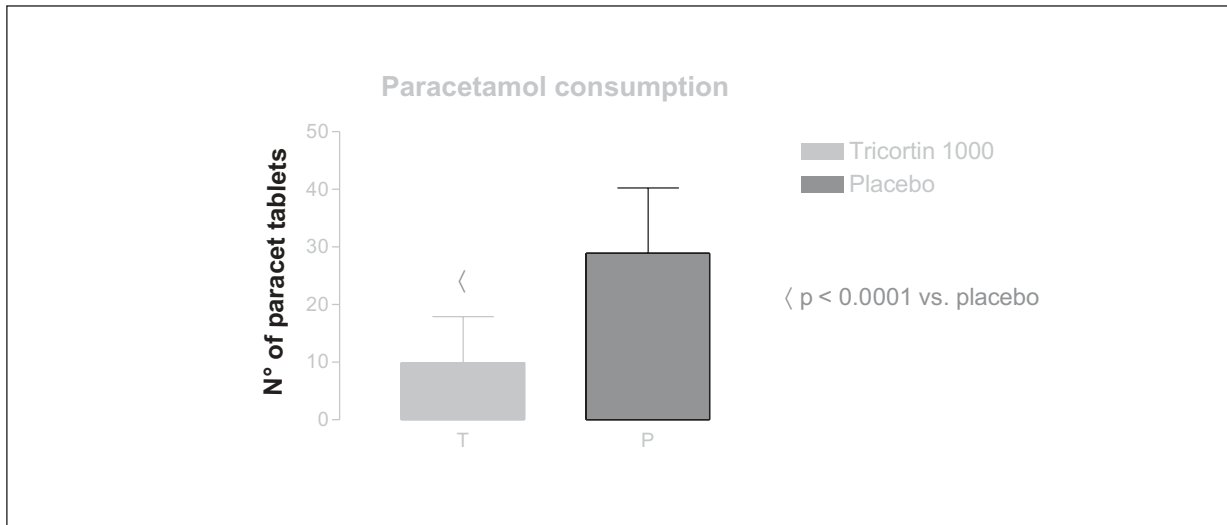


Figure 3.

currences of back pain. The authors conclude that the benefits of physical therapy or chiropractic manipulations may not be worth the costs.

NSAIDs are the therapy of choice in non-surgical patients, but the side effects of these drugs are well-known and may limit their use in selected patients.

Various studies of the clinical effects of Vitamin B₁₂ on painful vertebral syndromes,

indicating that this vitamin contribute to saving of NSAIDs by shortening the treatment time and reducing daily NSAID dosage, have been reported^{3,4,8}.

The benefits of Vitamin B₁₂ and its congeners has also been demonstrated in metabolic polyneuropathies, such as alcoholic polyneuropathy¹⁰, and uremic and diabetic neuropathy in patients receiving maintenance haemodialysis¹¹.

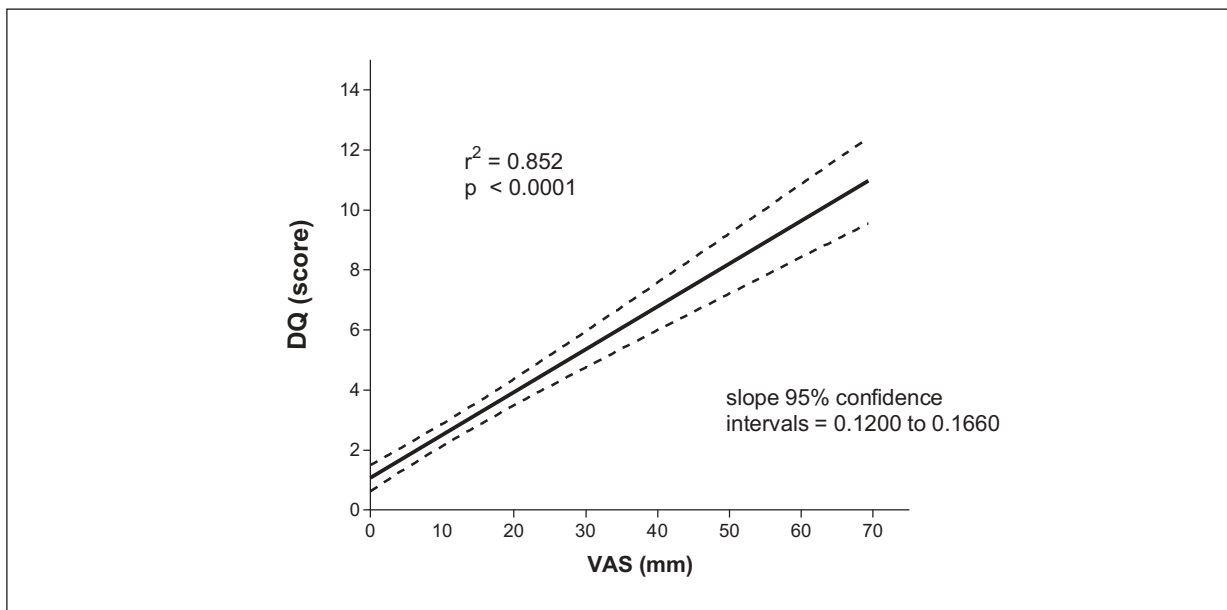


Figure 4.

Although the mechanisms producing these positive effects on nerve damage are not fully elucidated, it has been speculated that the accumulation of exogenous methylcobalamin promotes nerve regeneration or remyelination. Biochemical findings suggest that methylcobalamin acts directly as a methyl donor in DNA metabolism and that high concentrations up-regulate gene transcription, which may increase protein synthesis for nerve regeneration¹². These effects are not related with a Vitamin B₁₂ deficiency state.

Recently, a 4-year prospective study demonstrated the efficacy of methylcobalamin in preventing the deterioration of glaucomatous visual field defects non correlated with intraocular pressure, using the Cox proportional hazards model¹³. These results seem to indicate that the drug is able to slow the progression of optic nerve defects, another human model of peripheral neuropathy.

In the present study, the efficacy and safety of parenteral Vitamin B₁₂ in alleviating low back pain and related disability and in decreasing the consumption of paracetamol was confirmed in patients with no signs of nutritional deficiency. This low-cost regiment could easily be applied to outpatients, thus lessening the social burden of lost working days, and reducing the indirect cost of side effects related to NSAIDs.

References

- 1) BARTOSZYK GD, WILD A. B-vitamins potentiate the antinociceptive effect of diclofenac in carageenin-induced hyperalgesia in the rat tail pressure test. *Neurosci Lett* 1989; 101: 95-100.
- 2) FU Q-G, CARSTENS E, STELZER B, ZIMMERMANN M. B vitamins suppress spinal dorsal horn nociceptive neurons in the cat. *Neurosci Lett* 1988; 95: 192-197.
- 3) VETTER G, BRÜGGEMANN G, LETKO M, SCHWIEGER G, ASBACH H., et al. Verkürzung der Diclofenac-therapie durch B-vitamine. Ergebnisse einer randomisierten doppelblindstudie, Diclofenac 50 mg gegen Diclofenac 50 mg plus B-vitamine, bei schmerzhaften wirbelsäulenerkrankungen mit degenerativen Veränderungen. *Z Rheumatol* 1988; 47: 351-362.
- 4) KUHLEWEIN A, MEYER HJ, KOEHLER CO. Reduced need for diclofenac with concomitant B-vitamin therapy: Results of a double-blind clinical study with reduced diclofenac-dosage (75 mg diclofenac vs. 75 mg diclofenac plus B-vitamins daily) in patients with acute lumbago. *Klin Wochenschr* 1990; 68: 107-115.
- 5) YAMANE K, USUI T, YAMAMOTO T, et al. Clinical efficacy of intravenous plus oral methylcobalamin in patients with peripheral neuropathy using vibration perception threshold as an indicator of improvement. *Curr Ther Res Clin Exp* 1995; 56: 656-670.
- 6) SCOTT J, HUSKISSON EC. Graphic representation of pain. *Pain* 1976; 2: 175-784.
- 7) ROLAND M, MORRIS R. A study of the natural history of back pain. *Spine* 1983; 8: 141-144.
- 8) LETTKO M. Additive clinical efficacy of B-vitamins orally co-administered with NSAID diclofenac. In: *B-Vitamins in Pain* (HU Gerbershagen and M Zimmermann, Eds.), pp. 50-54, PMI Verlag, Frankfurt, 1988.
- 9) SHEKELLE PG. What role for chiropractic in health care? *N Engl J Med* 1998; 339:1074.
- 10) WOELK H, LEHRL S, BITSCH R, KÖPCKE W. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomised controlled study (BAP I Study). *Alcohol & Alcoholism* 1998; 33: 631-638.
- 11) KUWABARA S, NAKAZAWA R, AZUMA N, SUZUKI M, MIYAJIMA K. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. *Int Med* 1999; 38: 472-475.
- 12) PFOHL-LESZKOWICZ A, KEITH G, DIRHEIMER G. Effect of cobalamin derivatives on in vitro enzymatic DNA methylation: methylcobalamin can act as a methyl donor. *Biochemistry* 1991; 30: 8045-8051.
- 13) YAMAZAKI Y, HAYAMIZU F, TANAKA C. Effects of long-term methylcobalamin treatment on the progression of visual field defects in normal-tension glaucoma. *Curr Ther Res Clin Exp* 2000; 61: 443-451.