

B complex vitamins for analgesic therapy

O uso de vitaminas do complexo B em terapêutica analgésica

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ABSTRACT

BACKGROUND AND OBJECTIVES: The B complex vitamins have been used as single therapy or combined to other drugs, such as anti-inflammatory drugs, in different clinical situations, such as degenerative spinal diseases, rheumatologic diseases, polyneuropathies and in different postoperative situations. This study aimed at identifying in the scientific literature most recent evidences of the use of B complex vitamins as analgesic therapy and at describing clinical situations where their analgesic action could be observed.

CONTENTS: A search was carried out in Pubmed, Medline, LILACS, Cochrane Library and Scielo databases, contemplating the last 10 years and titles in Portuguese, Spanish and English. Keywords were: “pain”, “B complex vitamins”, “management”, “vitamin B1”, “vitamin B6”, “vitamin B12”, “thiamine”, “pyridoxine” and “cyanocobalamin”. Among 40 studies found, we have selected just musculoskeletal and neuropathic pain trials with humans, and where B complex vitamins were used as analgesic agents. From these, 13 studies were selected for meeting inclusion criteria. In all of them, B complex vitamins played roles in analgesia, even when in single therapy. B complex vitamins had also anti-inflammatory and anti-pruritus action, in addition to improving functionality.

CONCLUSION: Existing studies, although scarce and heterogeneous, have shown that B complex vitamins have analgesic effect. They are considered safe and have low cost and have shown to be a good option as adjuvant analgesic therapy.

Keywords: B complex vitamins, Management, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As vitaminas do complexo B têm sido utilizadas em monoterapia ou combinada a outros fármacos, como os anti-inflamatórios, em diversas situações clínicas, como por exemplo, nas doenças degenerativas da coluna, doenças reumatológicas, polineuropatias e nos pós-operatórios diversos. O objetivo deste estudo foi identificar na literatura científica as evidências mais recentes do uso de vitaminas do complexo B como terapia analgésica e descrever as situações clínicas em que se pode verificar a sua ação analgésica.

CONTEÚDO: Realizada a revisão bibliográfica na base de dados do Pubmed, Medline, LILACS, Biblioteca Cochrane e Scielo, contemplando os últimos 10 anos, títulos em português, espanhol e inglês. Os descritores utilizados foram: “Dor”, “vitaminas do complexo B”, “tratamento”, “vitamina B1”, “vitamina B6”, “vitamina B12”, “tiamina”, “piridoxina” e “cianocobalamina”. Dentre os 40 estudos encontrados selecionaram-se apenas os *trials* em dor musculoesquelética e neuropática com seres humanos, e em que as vitaminas do complexo B configuraram-se como agentes analgésicos. Foram selecionados então 13 estudos que satisfizeram esses critérios de inclusão. Em todos eles as vitaminas do complexo B desempenharam papéis na analgesia, inclusive quando em monoterapia. As vitaminas do complexo B também apresentaram ação anti-inflamatória, anti-pruriginosa, na funcionalidade e na qualidade de vida.

CONCLUSÃO: Os estudos existentes, apesar de heterogêneos, demonstraram que as vitaminas do complexo B possuem efeito analgésico em síndromes dolorosas neuropática e nociceptiva, e que por serem esses fármacos seguros e de baixos custos poderiam representar boas opções na terapêutica analgésica no nosso meio.

Descritores: Dor, Tratamento, Vitaminas do complexo B.

INTRODUCTION

B complex vitamins (Bvits) belong to the hydrosoluble group of vitamins, being made up of thiamine, riboflavin, niacin, niacinamide, pyridoxine, cobalamin, folic acid, pantothenic acid, biotin, choline, inositol and para-aminobenzoic acid (PABA). Among their major representatives to manage pain there are vitamins B1 (thiamine), B6 (pyridoxine) and B12 (cyanocobalamin)¹.

Bvits are important for nucleic acid and proteins synthesis, as well as for phosphatidylcholine synthesis. Phosphatidylcholine is a cell membrane phospholipid which is transformed in choline which shall be used for acetylcholine synthesis which is a major neurotransmitter²⁻⁴. Possible Bvits analgesic and anti-neuralgic mechanisms (especially vitamins B1 and B12) shown in experimental animal studies include: interaction with mediators caus-

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ing pain in nociceptors, increasing availability and effectiveness of norepinephrine and 5-hydroxytryptamine in pain inhibitory descending pathway; regeneration of damaged nerve fibers; stabilization of electric nervous excitability inhibiting ectopic discharges; and improved axonal transport, increasing nervous conduction velocity⁵⁻⁷.

For many years, Bvits have been used in monotherapy or combined with other drugs, such as anti-inflammatory drugs, in several clinical situations, such as degenerative spinal diseases, rheumatologic diseases, polyneuropathies (especially diabetic neuropathy) and in different postoperative periods¹⁻⁴. Notwithstanding several animal studies showing positive evidences of Bvits both for inflammatory and neuropathic pain, few human clinical trials have shown the same effects, which made Bvits analgesic efficacy controversial^{3,8}.

Cochrane Library has published in 2008 a review with 13 peripheral alcoholic and diabetic neuropathy trials, in a total of 741 participants, with emphasis to just one study with benfotiamine (derivative of vitamin B1). This study has observed a possible benefit of benfotiamine with slight increment on vibratory perception as compared to placebo. The review has stressed that high doses of Bvits are more effective than low doses, but the use of other therapies as compared to vitamins is more effective in the short term. So, it was suggested that further studies should be carried out to confirm the possible effect of Bvits on peripheral neuropathies⁹.

After Cochrane's publication, some studies were carried out to evaluate analgesic effects of Bvits in the management of nociceptive and neuropathic pain. So, due to more recent publica-

tions and still with questions about the real role of Bvits in the clinical practice involving different pain situations, this review is intended to update information on the use of such vitamins to manage pain.

This study aimed at identifying in the scientific literature most recent evidences of the use of Bvits as analgesic therapy and at describing clinical situations in which their analgesic action could be observed, both in monotherapy and in adjuvant therapy.

CONTENTS

This is a study carried out by means of integrative literature review, following the stages recommended for studies of this nature. Literature review was carried out in Pubmed, LILACS and Scielo databases, looking for scientific articles published in the last 10 years, from 2005 to 2015, in English, Portuguese and Spanish. Descriptors were "pain", "B complex vitamins", "management", "vitamin B1", "vitamin B6", "vitamin B12", "thiamine", "pyridoxine" and "cyanocobalamin". It should be stressed that these same descriptors were identified in DECS (Health Science Descriptors).

Narrative reviews and systematic reviews, experience reports, case reports and clinical trials were included in this scientific search. Among 40 studies found, we have selected just musculoskeletal and neuropathic pain trials with human beings, in which Bvits were used as analgesic agents.

We have selected 13 trials which have met herein established inclusion criteria. Table 1 is a summary of selected trials and their primary results.

Table 1. Clinical trials with vitamin B in musculoskeletal and neuropathic pain

| Authors | Type of trial | Sample | Objectives/Methods | Results/Conclusion |
|---|---|--|---|--|
| Ponce-Monter et al. ¹ | Randomized, controlled, Double-blind study | 122 patients aged between 18 and 55 years, with acute pain associated to lower limb fracture, VAS ≥ 50 mm | To compare the efficacy of diclofenac (75mg) associated to thiamine (100mg), pyridoxine (100mg) and cyanocobalamin (1mg), to diclofenac alone (same dose). Muscular injection 2 x/day, 24h before surgery and 24h after | Decreased pain in the first 4h (VAS >30 mm) in both groups. With association of vitamin B there has been further effectiveness as from 8h of the first application, being superiority maintained for 48h (p<0.05). Conclusion was that the association of vitamin B to diclofenac has increased its analgesic efficacy. |
| Mibielli et al. ⁷ | Randomized, controlled, Double-blind study | 372 patients, mean age of 66 years, with acute low back pain | To evaluate vitamins B1, 6 and 12 for pain. Randomization to diclofenac (50mg) + pyridoxine (50mg) + thiamine (50mg) + cyanocobalamin (1mg) (GDB), and diclofenac alone (50mg) (GD), by oral route 2x/day, for no longer than 7 days. | GDB has more effectively improved pain after 3 days, (decrease of ≥ 20 mm in VAS), and there has been personal satisfaction in this group. GDB was also better for functionality and mobility (p<0.05) |
| Maladkar, Tekchandani, Dave ¹⁰ | Open, exploratory, prospective, multicenter study | 497 patients aged between 40 and 75 years, with peripheral neuropathy of different origins | To evaluate the efficacy and safety of the associations of methylcobalamin (1500 μ g), alpha-lipolic acid (200mg), folic acid (5mg), biotin (5mg), benfotiamine (50mg) and vitamin B6 (5mg), 1x/day, O, for 12 weeks. | Major improvement of neuropathic symptoms already in the 4 th week. With 12 weeks there has been improvement in all symptoms (p<0.05): 78% pain decrease, 92.1% in numbness, 96.9% in muscle weakness, 96% in tingling and 99.2% in burning. The efficacy and safety of vitamin B associations for peripheral neuropathies was confirmed. |
| Negrão et al. ¹¹ | Open, exploratory, prospective, multicenter study | 212 patients aged between 19 and 92 years, with neuropathic pain of different origins | To evaluate the efficacy of vitamin B12 (3 μ g) associated to uridine monophosphate (50mg) and folic acid (400 μ g) simultaneously with regular use of analgesics (paracetamol, tramadol and anti-inflammatory drugs), O 1x/day, for 60 days. | Significant pain improvement according to Pain Detect (from 17.5 to 8.8 points), and of analgesic consumption in 75.6% of patients. The conclusion was that the association of vitamin B12, uridine and folic acid was effective for pain and also has allowed lower analgesic consumption. |

Continue...

Table 1. Clinical trials with vitamin B in musculoskeletal and neuropathic pain – continuation

| Authors | Type of trial | Sample | Objectives/Methods | Results/Conclusion |
|-----------------------------------|--|---|--|---|
| Talaei et al. ¹² | Randomized blind study | 100 patients between 18 and 53 years of age, with diabetic polyneuropathy | To compare the efficacy of vitamin B12 and nortriptyline on neuropathic symptoms. Randomization for 2 groups: 2000µg vitamin B12, IM 2x/ week or nortriptyline 10mg at night, for 3 months. | Better efficacy of vitamin B12 on pain, paresthesia and tingling, with statistical significance (p<0.001). without statistical significance in vibratory sensitivity, proprioception “pricking” and nervous conduction |
| Stracke et al. ¹³ | Randomized, controlled, double-blind study | 165 patients, aged between 42 and 73 years, with diabetic neuropathy | To evaluate the efficacy and safety of benfotiamine (Bf). Randomization for 3 groups: Bf 600mg/day, Bf 300mg/day and placebo for 6 weeks | Slight improvement of neuropathic symptoms with Bf, more pronounced with higher Bf dose. Conclusion was that Bf was a therapeutic option for diabetic polyneuropathy. |
| Xu et al. ¹⁴ | Randomized, controlled, blind study | 98 patients, age ≥ 50 years, with sub-acute, moderate to severe post-herpetic neuralgia, for at least 120 days. | To evaluate the efficacy of oral or local methylcobalamin for pain relief and DLA improvement. Randomization for 3 groups: methylcobalamin 1000µg SC 1x/day, lidocaine 1% SC 30mg 1x/day and methylcobalamin 0.5mg, O 3x/day, for 4 weeks. | SC methylcobalamin has progressively decreased pain, with superiority of this route as compared to oral route or to lidocaine in continuous paroxysmal pain or allodynia. The conclusion was that SC methylcobalamin was potential choice for sub-acute post-herpetic neuralgia. |
| Xu et al. ¹⁵ | Randomized, controlled, blind study | 90 patients between 55 and 92 years, with post-herpetic neuralgia for at least 120 days and pain NS of >4 in dermatomes T6 to T10 | To evaluate the efficacy of TENS combined to cobalamin applied in the painful area. Randomization for 3 groups: TENS + cobalamin, TENS + 1% lidocaine and TENS + cobalamin (1000µg cobalamin 40mg lidocaine). SC application in the largest painful area after each TENS session, 6 days a week for 8 weeks. | TENS + cobalamin or TENS + cobalamin + lidocaine have significantly improved pain (decrease ≥ 30%)(p<0.05). TENS + lidocaine have not significantly improved pain. There have been significant DLA increments with TENS + cobalamin and TENS + cobalamin + lidocaine, without statistically significant differences among them. |
| Xu et al. ¹⁶ | Randomized, controlled, blind study | 80 patients, age between 26 and 89 years, with com herpes zoster and pruritus score ≥ 4 for at least 20 days. | To evaluate the efficacy of local cobalamin and thiamine on pain, itching and DLA. Randomization for 4 groups: thiamine (100mg), methylcobalamin (1000µg), 1% lidocaine (30mg) and thiamine associated to cobalamin (100mg+1000µg. SC injections, 6 days a week, for 4 weeks. | There has been significant improvement in itching with thiamine, of pain with cobalamin and of both with the association of cobalamin and thiamine, in addition to improved DLA with cobalamin and cobalamin associated to thiamine. The conclusion was that thiamine had major anti-itching action, cobalamin analgesic action and the association of both had dual actions without synergy. |
| Chiu et al. ¹⁷ | Tandomized, controlled, double-blind study | 60 patients aged between 30 and 65 years, with non-specific chronic low back pain | To evaluate the efficacy and safety of methylcobalamin on pain and incapacity according to Oswestry index. Randomization for methylcobalamin 500µg and placebo, by muscular route, 3x a week, for 2 months | Methylcobalamin has significantly improved pain and incapacity as compared to placebo. Conclusion was that methylcobalamin was effective and safe for non-specific chronic low back pain. |
| Mibielli et al. ¹⁸ | Randomized, controlled, double-blind study | 81 patients, age between 18 and 65 years, with non-traumatic acute pain in lumbar, cervical or hip region | To compare the efficacy and safety of the association of diclofenac (70mg)/cholestyramine, nucleotides (uridine 1.5mg and cytidine 2.5mg) and hydroxycobalamin (1mg) with the association of nucleotides (uridine 1.5mg and cytidine 2,5mg) and hydroxycobalamin (1mg), O, 2x/day, for 10 days. | Pain improvement (decrease >30 mm in VAS) in approximately 87.5% of the diclofenac group (GD) and in 51.23% of the non-diclofenac group (GND), p>0.0006, improved functionality in 80% of GD and 29.3% of GND, p<0.0001. Conclusion was that GD was superior, but there has also been significant analgesia for GND |
| Garg, Syngle, Vohra ¹⁹ | Randomized, controlled, double-blind study | 30 patients between 43 and 72 years of age, with knee OA | To evaluate efficacy and tolerability of the association benfotiamine (50mg), pyridoxamine (50mg) and methylcobalamin (500µg) as compared to placebo, O, 3x/day, for 24 weeks | Statistically significant improvement of pain and clinical indices of disease activity, as well as decrease of one biomarker of disease activity (CRP) with vitamins. Conclusion was that the association of vitamins B1, 6 and 12 has improved functionality on DLA and joint mobility |
| Magaña-Villa et al. ²⁰ | Randomized, controlled, double-blind study | 48 patients, between 59 and 68 years of age, with severe knee AO (pain NS >7) in the preoperative period of arthroplasty | To evaluate efficacy and safety of diclofenac associated to vitamins B1, 6 and 12 (diclofenac 75mg, thiamine 100mg, pyridoxine 100mg and cyanocobalamin 5mg) compared to diclofenac (75mg) alone. Single muscular application 48h before surgery and pain evaluation for 12h | Analgesic superiority of the association of vitamins B1, 6 and 12 to diclofenac. There has also been increased analgesic duration for diclofenac in the preoperative period of arthroplasty (p<0.05) |

VAS = visual analog scale; O = orally; IM = intramuscular; SC = subcutaneous; NS = numeric scale; TENS = transcutaneous electric nerve stimulation; DLA = daily life activity; OA = osteoarthritis; CRP = C-reactive protein.

DISCUSSÃO

This study has reviewed recent publications and also published after a major Cochrane's systematic review from 2008 about the role of Bvits to manage peripheral neuropathies, time when available information were insufficient to determine the real clinical benefit of those vitamins as analgesics. We have found different results with more recent studies. It was observed that Bvits had significant analgesic effects in polyneuropathies, low back pain, osteoarthritis (OA) and post-herpetic neuralgias, both as adjuvant drugs and as monotherapy. In addition, Bvits had anti-inflammatory and anti-itching action, the latter in post-herpetic neuralgia patients and have also improved functionality. When those vitamins were associated to conventional acute or chronic pain management, they have decreased time for analgesic and anti-inflammatory drugs consumption, thus contributing to less deleterious adverse effects in some individuals^{1,7,10-20}.

The review of publications on Bvits for neuropathic pain, a total of 6 studies, point to beneficial effects, but with different doses and administration routes. Maladkar, Tekchandani and Dave¹⁰, studying peripheral neuropathic pain patients, have shown that after 12 weeks of Bvits administration (1500 µg methylcobalamin, 200mg alpha-folic acid, 5mg folic acid, 5mg biotin, 50mg benfotiamine and 5mg vitamin B6), there has been significant improvement of neuropathic symptoms. Negrão et al.¹¹ have also shown improved neuropathic pain after 60 days of daily use of vitamin B12 (3 µg) associated to uridine monophosphate (50mg) and folic acid (400mg), Talei et al.¹², using this same vitamin but in a dose of muscular 2000µg, twice a week for three months, have shown better efficacy of vitamin B12 as compared to nortriptyline (10mg) in diabetic polyneuropathy patients¹². Stracke et al.¹³, using benfotiamine (600 or 300mg, orally, once a day during six weeks) for diabetic neuropathy, have observed significant analgesic results, especially when higher doses were used. Other three studies, now addressing post-herpetic neuralgias, have shown that local subcutaneous cobalamin (1000µg once a day for 4 weeks) was superior to lidocaine to improve pain¹⁴⁻¹⁶.

So, it is suggested that the association of vitamins B12, B6 and B1, respectively and especially, in the doses of 1500µg (orally and daily) or 2000µg (muscular twice a week), of 50mg and of 300mg (both orally and daily), are effective as analgesic drugs for neuropathic pain.

As to publications about Bvits for nociceptive pain, 7 articles in total have also shown its analgesic effects. Chiu et al.¹⁷ have shown in chronic low back pain patients that vitamin B12 (500µg muscular, three times a week for two months) has improved pain and associated functional incapacity. Also, Mibielli et al.⁷ have shown that vitamins B12, B6 and B1 (50mg pyridoxine, 50mg thiamine, 1mg cyanocobalamin) associated to anti-inflammatory drugs (50mg diclofenac) have more effectively improved acute low back pain as compared to anti-inflammatory drug alone. And these same authors in a different study, now involving acute lumbar,

cervical and hip pain¹⁸, have shown that nucleotides (1.5mg uridine and 2.5mg cytidine) orally administered during 10 days, in association with vitamin B12 (1000µg) were effective in 51.23% of patients versus 87.5% when an anti-inflammatory drug (diclofenac) was associated to the same nucleotides; however, associations with anti-inflammatory drugs are related to further risk of adverse effects. So, vitamin B12 as analgesic adjuvant could be an alternative for acute back, cervical and hip pain when there are higher risks for the use of anti-inflammatory drugs. In other nociceptive pains such as knee OA and pain after limb fracture, Bvits have also shown analgesic effects^{1,19,20}, both alone and in association with anti-inflammatory drugs, in addition to benefits for inflammation (decreased C-reactive protein serum levels in monotherapy) and functional capacity^{19,20}.

Although observing a role of Bvits as analgesics in nociceptive pain, it was not possible to establish most effective doses, as it also was the case for neuropathic pain, because formulations and doses of studied trials were quite different. However, it seems that muscular associations in single doses of thiamine (100mg), pyridoxine (100mg) and cyanocobalamin (5000µg), or just the weekly use of methylcobalamin (1500µg) are good options, as well as benfotiamine (150mg), pyridoxamine (150mg) and methylcobalamin (1500µg) formulations, orally during 180 days.

In light of the above, there is still the need for further studies and better standardization to try to establish most effective doses, best administration routes and Bvits administration time for nociceptive and neuropathic pain syndromes. To date, it is suggested that higher doses for longer periods lead to better results.

CONCLUSION

Our review has counted on recent, however very heterogeneous studies, pointing to analgesic effects of Bvits in different neuropathic or nociceptive pain syndromes, as adjuvant or as monotherapy. So, Bvits, that are considered safe and have low cost, could be good options for pain management in Brazil.

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