

REVIEW ARTICLE

Efficacy and safety of combining NSAIDs with vitamin B for musculoskeletal pain: a systematic review and meta-analysis

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ABSTRACT

Musculoskeletal pain (MSP) is highly prevalent and impacts productivity, leading to significant economic and social burdens. Combining non-steroidal anti-inflammatory drugs (NSAIDs) with Vitamin B supplements has shown promising results in reducing MSP more effectively than NSAIDs alone. This meta-analysis aimed to assess the efficacy and safety of NSAIDs with Vitamin B, paving the way for future studies on the potential of Vitamin B as an add-on therapy for various MSP conditions. The relevant records up to June 2024 were retrieved from PubMed, Scopus, Web of Science, and the Cochrane Library. Two independent reviewers extracted data from eligible studies, including baseline data and information about the safety and efficacy of mixture regimens compared to using NSAIDs alone. Around 2,326 records were collected from four databases, excluding 189 duplicates. After screening titles and abstracts, 15 records were assessed for eligibility, resulting in eight included articles. Of these, six provided sufficient data for analysis, which compared NSAIDs alone vs. NSAIDs + Vitamin B for MSP, osteoarthritis, back pain, and cervical sprains. NSAIDs + Vitamin B significantly reduced visual analog scale pain scores [mean difference: -0.85 (95%CI: -1.33, -0.36; $p = 0.0007$)]. Adverse events were lower for NSAIDs + Vitamin B but not statistically significant [risk ratio: 0.77 (95%CI: 0.51, 1.18; $p = 0.23$)]. Combining NSAIDs with Vitamin B supplements showed promising benefits for MSP, offering more effective pain relief, earlier therapy termination, and improved functionality as compared to NSAIDs alone.

Keywords: Vitamin B, NSAID, musculoskeletal pain, back pain, meta-analysis.

Introduction

Musculoskeletal pain (MSP) can be acute or chronic, affecting muscles, bones, ligaments, tendons, and nerves [1]. It affects a large part of the global population, with varying prevalence rates among different demographics and occupational groups. Studies have reported the prevalence of MSP in the general population, ranging from 13.7% to 97% [2-4]. Occupational groups, such as healthcare workers, can have an MSP prevalence of up to 97%, with neck and lower back pain being common complaints [5]. Specific populations like postmenopausal women, medical students, and construction workers also experience high prevalence rates [6-8]. Furthermore, MSP impacts individuals of all ages, with women typically demonstrating higher prevalence when compared to men [9].

MSP significantly impacts work productivity and the economy, leading to decreased socialization, work incapacity, loss of independence, anxiety, depression,

and future concerns [10]. The economic burden of musculoskeletal disorders, such as chronic low back pain and osteoarthritis, is substantial and affects families, society, and healthcare systems [11-13]. They result in longer recovery periods, work absence, increased medical expenses, and social costs, severely affecting individuals' quality of life and leading to long-term disability [14]. The economic burden emphasizes the

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need for effective management strategies, as treatment failures and associated costs pose challenges for patients, healthcare providers, and systems [15,16].

MSP mechanisms depend on the underlying etiology. For instance, Osteoarthritis, a degenerative joint disease, significantly contributes to MSP by thinning cartilage fibers in the joints, leading to stiffness, pain, and impaired joint function [17]. It is a leading cause of chronic MSP and mobility disability, particularly affecting elderly populations worldwide [18]. The chronic nature of osteoarthritis makes it a challenging condition to manage effectively [19]. Another example is back pain, a prevalent and disabling musculoskeletal disorder linked to maintained and repetitive loads, mechanical stress, inflammation of tendons, degeneration of joints, painful muscle spasms, and intervertebral disc issues, all contributing to MSP [20].

Medical options for managing MSP include non-pharmacological treatments, complementary therapies, and pharmacological interventions. Non-pharmacological treatments, such as patient education, self-management strategies, exercise therapy, and massage therapy, are commonly used to alleviate pain and improve function. Complementary therapies, like acupuncture, have also shown effectiveness in pain management [21]. Pharmacological interventions play a crucial role and include medications such as non-steroidal anti-inflammatory drugs (NSAIDs), simple analgesics, opioids, and adjuvants [21,22]. Another commonly employed option is multimodal analgesia, which combines different classes of medications for enhanced pain relief [1].

NSAIDs are pivotal in managing MSP by inhibiting the cyclooxygenase (COX) enzyme, hence reducing inflammation and pain associated with conditions like osteoarthritis and rheumatoid arthritis [23,24]. Nevertheless, the use of NSAIDs might be complicated by side effects such as gastrointestinal toxicity [25]. Vitamin B supplements include thiamine (B1), pyridoxine (B6), and cyanocobalamin (B12). The various forms of Vitamin B play a critical role in pain management and inflammation modulation. These vitamins synergistically improve neuropathy, motor control, nociceptive responses, and neuropathic pain [26]. Thiamine alleviates neuropathic pain and reduces allodynia, while pyridoxine enhances diclofenac's analgesic effects and mitigates symptoms like hand-and-foot syndrome in cancer patients [27-29]. Moreover, thiamine and cyanocobalamin have shown efficacy in chronic cluster headache relief, and pyridoxine has been effective in managing premenstrual syndrome and dysmenorrhea symptoms [30-32].

Multimodal analgesia using a combination of NSAIDs and vitamin B has been explored in a few studies [33-35]. The effect on different types of pain, such as back pain and osteoarthritis, was reported to be superior to the use of NSAIDs alone [33,36]. This review aimed to investigate the efficacy and safety of NSAIDs + Vitamin B and how it compares to using NSAIDs alone across various musculoskeletal conditions. By exploring the potential benefits, this review paved the road for future studies to investigate the use of Vitamin B supplements

as add-on therapy alongside NSAIDs for various causes of MSP.

Subjects and Methods

The current review was completed as per the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Handbook for Systematic Reviews of Interventions [37,38].

Eligibility criteria

Articles containing conditions leading to MSP, observational or interventional studies investigating the effect of NSAID + Vitamin B on MSP, articles written in the English language, and articles that were retrieved in the full text were included. Abstracts, letters to editors, comments, case reports, single-arm studies, reviews, animal studies, and articles written in languages other than English were all excluded.

Information sources and search strategy

The process of retrieving records involves multiple steps. Initially, broad search terms were utilized to explore databases for pertinent articles. Following the initial search, a thorough search strategy was formulated encompassing all relevant terms and their MeSH equivalents. In the subsequent phase, targeted searches were conducted using specific terms related to MSP and various combinations of NSAIDs and vitamin B across PubMed, Scopus, Cochrane Library, and Web of Science.

The final search strategy was formulated with the following: NSAID (with its variants like diclofenac, fenoprofen*, coxib*, COX 2 inhibitor*, medicine names, and CAS numbers) AND Vitamin B12 (with its variants and medicine names) AND musculoskeletal and its variants (low back pain, painful spinal diseases, fracture, sciatica, Analges*, and so on).

Using the detailed query, the final search strategy was applied in June 2024. Finally, the retrieved records' references and citations were manually searched for additional relevant studies.

Selection process

Two independent reviewers meticulously examined the titles and abstracts of all available records to ensure a thorough screening process. Before handing records to reviewers, identifying data were removed, such as author names and affiliations, to guarantee an impartial assessment. Both reviewers adhered to specific eligibility criteria designed to guide them through the screening. In the event of conflicts, a third reviewer collaborated with the initial reviewers to resolve any discrepancies that arose during the process. Subsequently, the same two reviewers evaluated the eligibility of articles from the screening step in full text, engaging in detailed discussions to address any disputes that arose during the process.

Data collection

Two independent reviewers extracted relevant data from all available full-text articles into a spreadsheet using

a predefined set of variables. This involved extracting baseline information from the eligible studies, such as the author's last name, study arms, and design, country of origin, follow-up duration, etiology of pain, treatment regimens, and primary outcomes. In addition, the number of patients, their age, and gender distribution were extracted. For analysis, data related to pain intensity and the rate of adverse events was extracted. All outcomes were extracted at baseline and subsequent follow-up visits for both NSAID + Vitamin B (Treatment arm) and NSAID alone (Control arm). Conclusions from each study were collected to summarize their findings.

Outcome measures

All variables were presented as Mean $\pm$ SD. Change scores were calculated by finding the difference between the follow-up and baseline values. If data were expressed differently, the formula from the Cochrane Handbook was used to convert them into means and standard deviations.

Visual Analogue Scale (VAS) score for pain

The VAS was commonly used to assess pain in different medical settings. It involves a 100 mm line, where one end indicates "no pain" and the opposite indicates "worst imaginable pain." Patients mark on the line the point that best represents their current pain level. This provides a subjective but quantifiable measure of pain intensity [39]. All measurements were in the range from 0 to 10.

Adverse effects

The number of adverse events reported on the same follow-up visit where pain data were extracted was also considered.

Risk of bias

Two separate reviewers evaluated the quality of the full-text articles, and a third reviewer resolved any conflicts. The methodical quality of all non-randomized controlled trials was assessed using the ROBINS-I tool [40]. Similarly, the RoB2 provided by Cochrane was used to evaluate all Randomized control trials (RCTs) included in the review [41].

Statistical analysis

All data were analyzed using RevMan v5.4.1 software to determine the mean difference (MD) in change scores from baseline between the treatment and control arms. The efficacy of each regimen was compared in reducing pain severity as measured by the VAS score. Similarly, the risk ratio (RR) for adverse events was computed in both groups. The corresponding 95% confidence intervals (CIs) were reported alongside the pooled effect sizes. Statistical significance was considered at a *p*-value of less than 0.05. The heterogeneity among the included studies was assessed using the *I*² statistic, where values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively. Significant heterogeneity was defined as an *I*² value exceeding 50% combined with a *p*-value of less than 0.05. The random effects model was used to account for differences between populations and

inclusion criteria of the eligible articles. The results were illustrated on a forest plot, which contained information about individual studies and the heterogeneity of the effect measure. Sensitivity analysis was undertaken for all studies with outlier effect sizes.

Results

Study selection

After searching through four databases, 2,326 records were collected. After removing 189 duplicates, 2,137 unique records were left. The titles and abstracts were then screened, excluding 2,122 entries. The full text of the remaining 15 records was obtained and assessed against the eligibility criteria. During this assessment, one animal study, four non-English articles, and two articles that did not meet the specified population criteria were excluded. Ultimately, eight articles were included in the review, of which six provided enough data to be included in the analysis (Figure 1).

Characteristics of the included studies

The current review comprises eight articles; six randomized controlled studies, one non-randomized controlled study, and one *post hoc* analysis [33-36, 42-45]. Seven studies compared the NSAID + Vitamin B regimen vs. NSAID alone, and one study compared it to the NSAID + codeine regimen. The mean age of participants was 44.96 years, and 49.9% were males. The follow-up period varied drastically between studies, ranging from as little as 90 minutes to 2 years. The underlying etiology for pain was back pain in three studies, osteoarthritis in three studies, and cervical sprain and limb injury in one study. The components of vitamin B therapy in the treatment are varied among studies; Vitamin B 1 + 6 + 12 (5 studies), Vitamin B 1 (2 studies), and Vitamin B 1 + 2 + 3 + 6 + 12 (1 study) (Table 1).

Risk of bias

Reviewers used assessment tools to rate studies according to their risk of bias. The seven randomized controlled trials were evaluated using the RoB2 tool. Overall, four studies had a low risk of bias, two trials had some concern, and a single study had a high risk of bias. The only non-randomized trial was determined to have had a high risk of bias using the ROBINS-I tool (Figure 2 and Supplementary File 1).

Results of syntheses

Five studies explored the difference in pain scores after administration of NSAIDs alone vs. NSAIDs + Vitamin B. The underlying cause of pain was osteoarthritis in three studies [33,43,44], back pain in one study [45], and cervical sprains in another study [34]. Overall, the NSAIDs + Vitamin B combination was significantly superior to the use of NSAIDs alone, with an MD reduction in VAS scores of -0.85 [95%CI: -1.33, -0.36; *p* = 0.0007]. Since the study by Magaña-Villa et al. [44] differed significantly from other studies, possibly due to the very brief follow-up period, the analysis again was performed after excluding it. However, the removal of

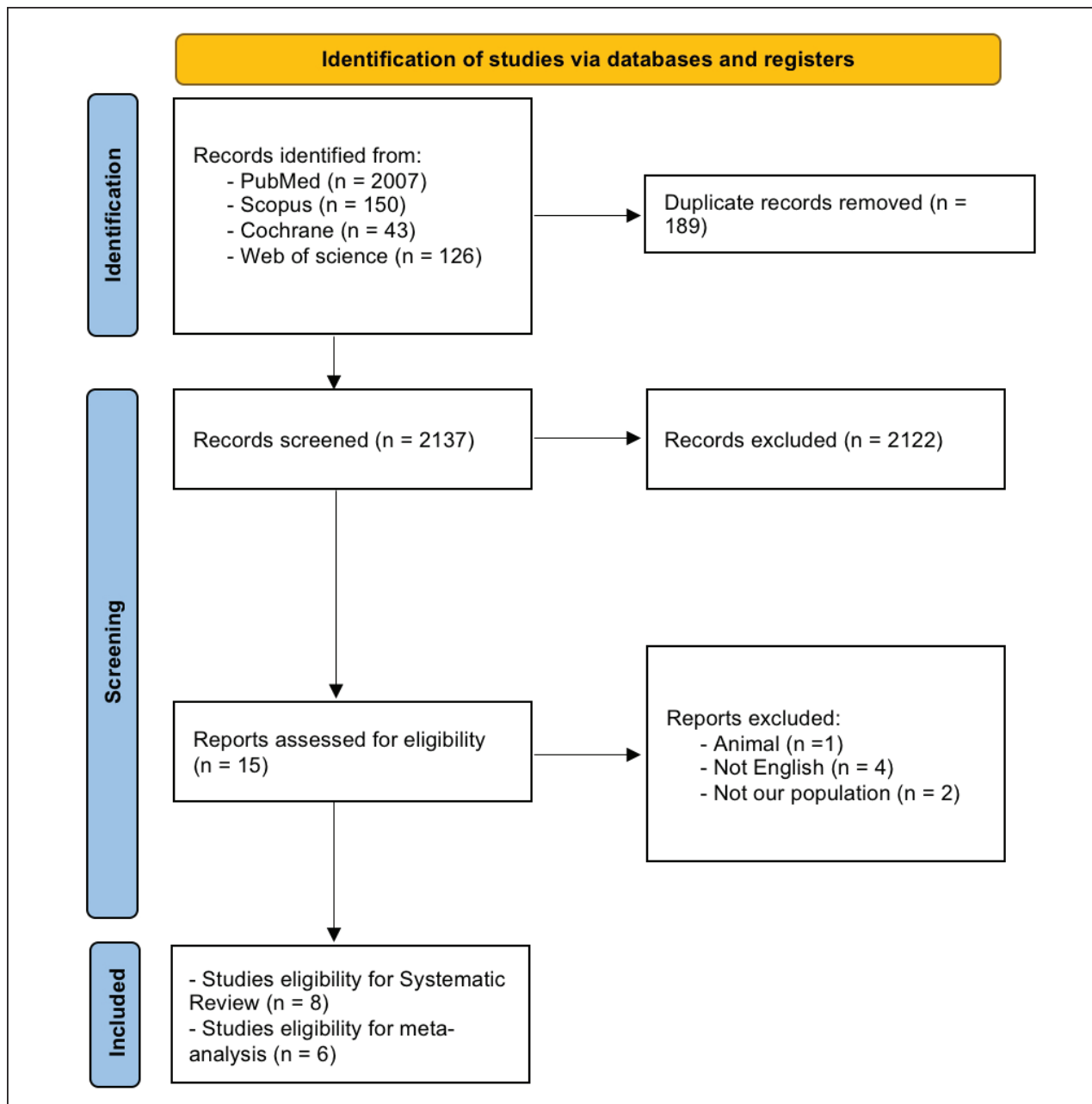


Figure 1. PRISMA Flow diagram.

the study did not affect the significance of the effect size -0.57 [95%CI: $-0.86, -0.28$; $p = 0.0001$] [44]. Conversely, the rate of adverse events was compared between the three studies using both preparations. The risk of adverse events was slightly lower for NSAIDs + Vitamin B than it was for NSAIDs alone [RR: 0.77 ; 95%CI: $0.51, 1.18$; $p = 0.23$]; however, the results were not statistically significant (Figures 3-5).

Adverse events

The details of adverse effects of NSAID + vitamin B versus NSAID alone were as follows. Delgado-García et al. [34] reported 45 adverse events in 36 patients, with the dexketoprofen group experiencing a higher percentage of moderate adverse events compared to the dexketoprofen/vitamin B group (41.4% vs. 6.2%). Gastrointestinal

disorders were more common in the dexketoprofen group (64.3%) compared to the dexketoprofen/vitamin B group (35.7%) [34]. Mibielli et al. [45] revealed that adverse events commonly associated with NSAID treatment were observed during the study. Three patients withdrew from the study due to temporary elevation of transaminases and dyspepsia. However, there were no clinically significant differences between the groups in terms of vital signs and laboratory values [45]. Kaur et al. [43] observed mild side effects such as dyspepsia, flatulence, diarrhea, nausea, and headache at 4 weeks, which did not persist up to 8 weeks, and these side effects were comparable between both groups.

Onset of effect

The efficacy of NSAID combined with vitamin B was assessed across three studies. Mibielli et al. [45] reported

Table 1. Summary and baseline characteristics of the included studies.

Study ID	Intervention, N	Study design	Country	Age	Male, N (%)	Followup	Treatment regimen	Etiology of the pain	Inclusion criteria	Primary outcomes	Conclusion
Delgado-García et al. [34]	NSAID + Vitamin B, 83	Randomized clinical trial	Mexico	40.2 ± 17.3	30 (36.1%)	7 Days	Dexketoprofen 25 mg/vitamin B capsule (thiamine 100 mg, pyridoxine 50 mg, cyanocobalamin 0.50 mg)	Patients with grade I-II cervical sprains, according to the Quebec scale	1. Participants were required to be at least 18 years of age at the beginning of the study. 2. The study included participants diagnosed with grade I or II cervical sprain on the Quebec scale 3. With ≤3 days of evolution, and whose evaluation of the VAS was ≥4 cm. 4. Women of childbearing age currently using an approved contraceptive method, such as barrier, hormonal, injectable, subdermal, menopausal, or surgically sterile	1. Pain intensity by VAS. 2. Northwick Park neck pain questionnaire. 3. Adverse events	"The fixed-dose combination of dextetoprofen/thiamine + pyridoxine + cyanocobalamin vitamins demonstrated superior efficacy and a better safety profile compared with dextetoprofen monotherapy for pain treatment in patients with grade I-II cervical sprains."
	NSAID, 87			43 ± 12.8	29 (33.3%)		dexketoprofen 25 mg tablet (orally, every 8 hours, for 7 days)				
Gaydukova et al. [35]	NSAID + Vitamins B, 50	Non-randomized clinical trial	Russia	-	-	2 Years	NSAID + vitamins (B1, B6, B12)	Chronic back pain	1. Presence of confirmed diskogenic pain syndrome and signed informed consent to participate in the study.	1. Pain intensity by NRS	"Continuation of effective anti-inflammatory treatment was associated with the use of coxibs, use of Neurobion, normal body weight, and achievement of reductions in pain syndrome even if complete resolution was not attained. Increases in treatment compliance could be achieved by increasing efficacy by using NSAID (especially coxibs) in complex with group B vitamins (B1, B6, B12), normalization of body mass index, and effective control of liver function."
	NSAID, 148						NSAID				
Geller et al. [36]	NSAID + Vitamin B, 187	Post-hoc analysis	Brazil	38.1 ± 9	100 (%)	7 Days	diclofenac (50 mg) and vitamins B1 (thiamine mononitrate, 50 mg), B6 (pyridoxine hydrochloride, 50 mg) and B12 (cyanocobalamin, 1 mg)	Low back pain (LBP) or lumbago	1. Subjects were between 18 and 65 years of age. 2. Subjects with a clinical presentation of acute, non-traumatic lumbago lasting no longer than 3 days. 3. And with a VAS (0-100 mm) between 20 and 80 mm. 4. Pre-menopausal female subjects were required to submit a urine pregnancy test and maintain adequate birth control for the duration of the study.	1. Pain intensity by VAS. 2. Finger-to-floor distance. 3. Schober test.	"The results of this post-hoc analysis show that combination therapy with diclofenac plus vitamins B1, B6, and B12 had additional positive effects on mobility restoration among the patients of the DOLOR study and served to highlight the correlation between mobility and pain intensity among patients presenting with low back pain. The two fundamental goals of low back pain therapy are to provide improvements in pain and function. In this sense, combining diclofenac with the B vitamins was particularly effective in achieving both goals."
	NSAID, 185			36 ± 9	99 (%)		diclofenac (50 mg)				

(Continued)

Study ID	Intervention, N	Study design	Country	Age	Male, N (%)	Followup	Treatment regimen	Etiology of the pain	Inclusion criteria	Primary outcomes	Conclusion
Graudins et al. [42]	NSAID + Vitamins B, 61	Randomized clinical trial	Australia	35 ± 17	42 (68.9%)	90 minutes	Two tablets x paracetamol 500 mg, Two tablets x ibuprofen 200 mg, Two tablets x thiamine 100 mg	Pain from limb injury	1. Age 18-75 years 2. Acute limb injury (previous 48 hours) 3. Moderate pain on arrival (numerical rating 4 to 7 on a 0 to 10 scale) 4. Oral analgesia deemed suitable.	1. Pain intensity by VAS. 2. Patient-reported satisfaction. 3. Adverse events.	"For a convenience sample of adult ED patients with moderate pain from limb injury, the present study found that the non-opioid, codeine, and oxycodone groups were all non-inferior at the primary outcome time of 30 min. This supports the initial use of a non-opioid combination for moderate pain from limb injury. Duration of adequate analgesic effect, different non-opioid drug and dosage regimens, and effectiveness in other conditions all warrant further investigation."
	NSAID + Codeine, 62			32 ± 16.7	40 (64.5%)		Two tablets x paracetamol 500 mg, Two tablets x ibuprofen 200 mg, Two tablets x codeine 30 mg				
Kaur et al. [43]	NSAID + Vitamin B, 65	Randomized clinical trial	India	56.95 ± 9.61	106 (82%)	56 Days	Diclofenac 75 mg orally daily along with Vitamin B complex tablet (thiamine 10 mg, riboflavin 10 mg, nicotinamide 45 mg, pyridoxine 3 mg, cyanocobalamin 15 µg, and calcium pantothenate 50 mg) orally daily for 4 weeks in the morning after breakfast	Patients with Primary osteoarthritis of the knee	1. Diagnosed cases of primary OA knee of either sex. 2. >40 years of age, having grade 2 and 3 osteoarthritic changes on radiological imaging according to Kellgren–Lawrence classification and patients with unilateral and bilateral knee involvement with a VAS score >5 at baseline.	1. Pain intensity by VAS. 2. Western ontario and McMaster Universities Osteoarthritis Index. 3. Adverse events.	"The present study suggested that Vitamin B complex as an add-on therapy was found to cause a significant reduction in pain score. It could be a promising drug in patients with OA to improve the analgesic effect, when combined can reduce the dose of diclofenac, thereby minimizing the side effects."
	NSAID, 65			57.48 ± 11.36			75 mg diclofenac tablet orally daily for 4 weeks in the morning after breakfast				
Magaña-Villa et al. [44]	NSAID + Vitamin B, 24	Randomized clinical trial	Mexico	61.2 ± 1.8	9 (37.5%)	0.5 Day	a single intramuscular injection of sodium diclofenac (75 mg) combined with thiamine (100 mg), pyridoxine (100 mg) and cyanocobalamin (5 mg).	Patients with osteoarthritis	1. Patients with severe osteoarthritis 2. Pain level ≥7	1. Pain intensity by VAS. 2. Adverse events.	"This study constitutes a clinical support on the improvement of the analgesic effect of diclofenac by B vitamins in patients with osteoarthritis programmed to total knee arthroplasty, as a clinical model of inflammatory pain."
	NSAID, 24			65.6 ± 3.1	7 (29.17%)		a single intramuscular injection of sodium diclofenac (75 mg) alone				

(Continued)

Study ID	Intervention, N	Study design	Country	Age	Male, N (%)	Followup	Treatment regimen	Etiology of the pain	Inclusion criteria	Primary outcomes	Conclusion
Mibielli et al. [45]	NSAID + Vitamin B, 187	Randomized clinical trial	Brazil	38.1 ± 9	100 (%)	7 Days	Tablets containing: 50 mg of diclofenac, 50 mg of thiamine mononitrate (B1), 50 mg of pyridoxine hydrochloride (B6), and 1 mg of cyanocobalamin (B12)	LBP or lumbago	- Subjects were between 18 and 65 years of age. - Subjects with a clinical presentation of acute, non-traumatic lumbago lasting no longer than 3 days. - And with a VAS (0-100 mm) between 20 and 80 mm. - Pre-menopausal female subjects were required to submit a urine pregnancy test and maintain adequate birth control for the duration of the study.	- Pain intensity by VAS. - Finger-to-floor distance. - Adverse events.	"The combination of diclofenac with B vitamins was superior to diclofenac monotherapy in lumbago relief after 3 days of treatment. As a study drawback, daily VAS measurements were only recorded until the subject withdrawal from treatment, whether after 3, 5, or 7 days. There were no differences in safety profile between the two study groups."
	NSAID, 185			36 ± 9	99 (%)		tablets containing 50 mg of diclofenac.				
Dehghan et al. [33]	NSAID + Vitamin B, 38	Randomized clinical trial	Iran	1. 30-40, 11 (28.9%) 2. 40-50, 13 (34.2%) 3. 50-60, 14 (36.8%)	17 (44.7%)	21 Days	Oral diclofenac 50 mg twice a day and B complex tablet 100 mg	Patients with primary osteoarthritis of the knee	- The age of 30-60 years. - Diagnosis of primary knee osteoarthritis by an orthopedics (per descriptions, clinical symptoms, physical examinations, radiologic and relevant diagnostic criteria of this disease).	- Pain intensity by VAS. - Western Ontario and McMaster Universities Osteoarthritis Index. - Adverse events	"In view of similar analgesic and anti-inflammatory properties, as well as very few, non-prevalent complications of B and E vitamins, use of two or more drugs with a different mechanism of effect seems necessary to enhance their effect on osteoarthritis treatment."
	NSAID, 35			1. 30-40, 7 (20%) 2. 40-50, 16 (45.7%) 3. 50-60, 12 (34.3%)	15 (42.9%)		Oral diclofenac 50 mg twice a day				

that after 3 days of treatment, 46.5% of subjects in the NSAID + vitamin B group could terminate treatment compared to 29.7% in the NSAID alone group, with a

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Delgado-García 2024	+	+	+	+	+	+	+
Geller 2016	+	+	+	+	+	+	+
Graudins 2016	+	+	+	+	+	+	+
Kaur 2021	+	?	-	-	+	+	+
Magaña-Villa 2013	?	?	+	?	+	+	+
Mibielli 2009	+	+	+	+	+	+	+
Morteza Dehghan 2015	?	?	+	?	+	+	+

Figure 2. Risk of bias summary of the included RCTs.

statistically significant difference. After 5 days, 82% of the combination group could terminate due to treatment success versus 43% of the NSAID group. At 7 days, both groups showed similar success rates in concluding treatment [45]. Magaña-Villa et al. [44] found that the combination treatment led to a significantly better reduction in VAS pain scores, starting at 0.5 hours and lasting up to 12 hours, compared to NSAID alone. The mean area under the VAS curve for the combination group was significantly lower, indicating better overall pain management [44].

Discussion

MSP is a potentially disabling condition with far-reaching economic and social implications [10]. It affects up to 97% of the population, leading to impaired productivity, work absence, family affection, and increased medical costs [10-13]. Innumerable conditions might cause acute or chronic MSP, with osteoarthritis, back pain, and neck pain being the leading underlying etiologies [4,17,33].

In this review, the effect of combining NSAIDs with different mixtures of Vitamin B supplements compared to using NSAIDs alone were investigated. It was found that adding Vitamin B supplements to existing NSAID regimens reduced the pain more effectively than using NSAIDs alone as measured by VAS 0-10 score (MD: -0.85), and the effect was statistically significant ($p < 0.001$). Furthermore, adding Vitamin B supplements improved short-term pain relief in less time and helped patients terminate therapy earlier than using NSAIDs alone [44,45]. The number of patients developing adverse events was lower for the Vitamin B group; however, the RR was not statistically significant between the two groups.

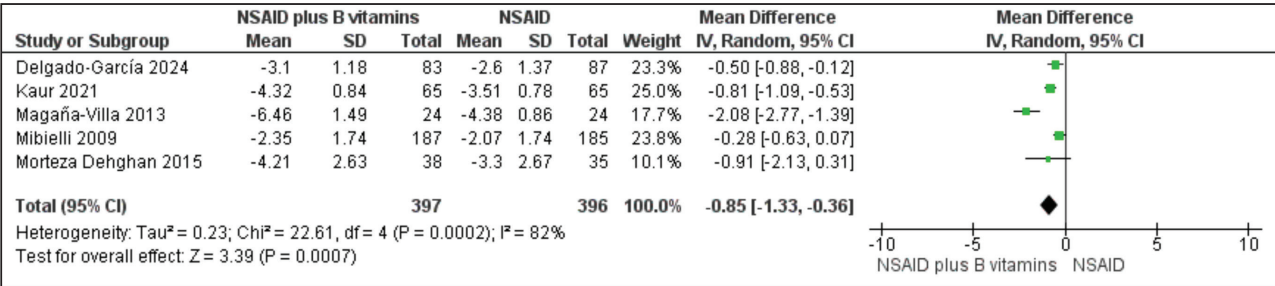


Figure 3. Forest plot of pain by VAS score.

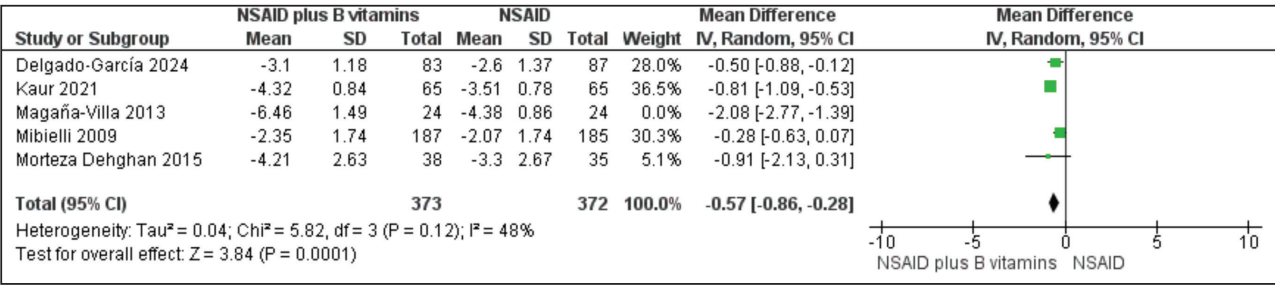


Figure 4. Forest plot of pain by VAS score after excluding one study.

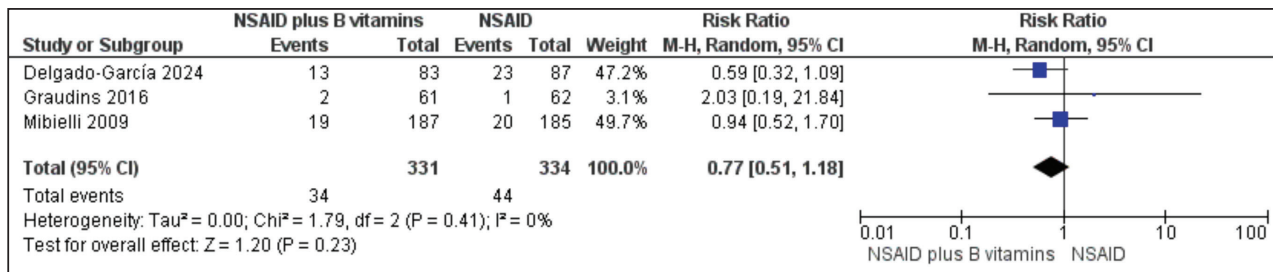


Figure 5. Forest plot of adverse events incidence.

The studies in this review focused mainly on the effect of including Vitamin B in existing regimens for back pain and osteoarthritis. The addition of vitamin B to NSAID regimens has demonstrated significant benefits in managing osteoarthritis. Magaña-Villa et al. [44] found that combining vitamin B with diclofenac significantly improved the pain reduction profile, with earlier and greater decreases in VAS pain scores compared to diclofenac alone. Kaur et al. [43] reported that adding vitamin B to diclofenac resulted in a statistically significant reduction in pain scores at 4 and 8 weeks, potentially reducing NSAID dosage and, thereby, the related side effects. Similarly, Dehghan [33] indicated that the vitamin B group experienced more significant improvements in knee pain VAS, total pain severity, and past 48-hour function compared to the diclofenac and vitamin E groups.

Using Vitamin B supplements for back pain led to similar effects. Mibielli et al. [45] demonstrated that patients treated with a combination of diclofenac and B vitamins had higher rates of treatment success, earlier pain relief, and greater pain intensity and mobility improvements compared to those treated with diclofenac alone [45]. The study also reported a greater reduction in VAS pain scores and improved functionality, with a good safety profile. Geller et al. [36] found that adding B vitamins to diclofenac significantly improved Finger-to-Floor Distance and Schober's test scores. Conversely, Gaydukova et al. [35] reported that the use of B vitamins in combination with NSAIDs was associated with higher treatment compliance and effectiveness, particularly in patients with severe pain, obesity, and nonalcoholic fatty liver disease.

Reducing the dose of NSAIDs can have a significant impact on the rate of adverse effects associated with their use. There was no clear evidence supporting an increased risk of adverse effects with prolonged NSAID administration, which shifted the focus toward dose reduction as a possible clinical approach [46]. The risk of gastrointestinal complications with traditional NSAIDs was present from the first dose; hence, lower doses of oral NSAIDs, such as diclofenac and etoricoxib, had more favorable safety profiles compared to the maximum recommended daily doses while still maintaining significant treatment effects [47,48].

Adding B vitamins to NSAID therapy can potentially have beneficial effects. B vitamins, including folate, B6, and B12, were shown to effectively modify high plasma

homocysteine levels, increasing cardiovascular risk [49]. A study by Pérez-Jimenez et al. [50] found that combining B vitamins with NSAIDs produced a synergistic effect, enhancing the analgesic and anti-inflammatory effects of NSAIDs and potentially reducing adverse effects by allowing for lower NSAID doses. This synergistic effect could be particularly useful in reducing the risk of adverse events associated with NSAID use.

Despite being the first review to cover the potential benefits of combining Vitamin B with NSAIDs, a very high heterogeneity was faced in the efficacy outcome. This might be attributed to multiple factors, including the variations in the underlying etiologies of MSP and combinations of Vitamin B, as well as differences in dosing and routes of administration. In addition, there were not enough studies comparing adverse events between both regimens, which might have caused the results to be non-significant. Given the widespread use of NSAIDs for various MSPs, which are often accompanied by multiple side effects, there is potential for Vitamin B mixtures to reduce the dosage and duration of NSAID therapy. Future studies should focus on investigating the optimal combination and dosage of Vitamin B supplements to achieve pain relief and minimize the side effects of NSAIDs in different skeletal conditions.

Conclusion

This review emphasizes the promising benefits of combining NSAIDs with Vitamin B supplements for managing MSP, especially in cases of osteoarthritis and back pain. The addition of Vitamin B supplements to NSAID regimens resulted in more effective pain relief, earlier termination of therapy, and improved functionality compared to using NSAIDs alone. While the combination demonstrated a good safety profile, the review also noted high heterogeneity in efficacy outcomes and a lack of comprehensive studies on adverse events. Therefore, future research should aim to determine the optimal combination and dosage of Vitamin B supplements to maximize pain relief and minimize NSAID-related side effects across various musculoskeletal conditions.

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List of Abbreviation

None.

Conflict of interests

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Supplementary Material

		Risk of bias domains							
Study	Gaydukova 2019	D1	D2	D3	D4	D5	D6	D7	Overall
									
		Domains: D1: Bias due to confounding. D2: Bias due to selection of participants. D3: Bias in classification of interventions. D4: Bias due to deviations from intended interventions. D5: Bias due to missing data. D6: Bias in measurement of outcomes. D7: Bias in selection of the reported result.						Judgement  Serious  Moderate  Low	

Supplementary File 1. Risk of bias assessment using ROBINS-I tool.