Ibraheem Algarni et al. Saudi J Er Med. 2025;6(1):326-338
DOI: 10.24911/SJEMed.72-1725634958

REVIEW ARTICLE

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

Ibraheem Algarni[1]*, Ahmed A. Alfayez[2], Hussain A. Alharbi[3], Waleed K. Alsobhi[3], Abdulaziz A. Dhelemi[3], Malak N. AlShebel[4], Mousa M. Al anazi[5], Ziyad M. Alqurayqiri[6], Turki M. Alharbi[6]

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

Correspondence to: Ibraheem Algarni
*Department of Family and Community Medicine, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
Email: ialgarni@kau.edu.sa
Full list of author information is available at the end of the article.
Received: 06 September 2024 | **Accepted**: 12 November 2024

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 ± 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

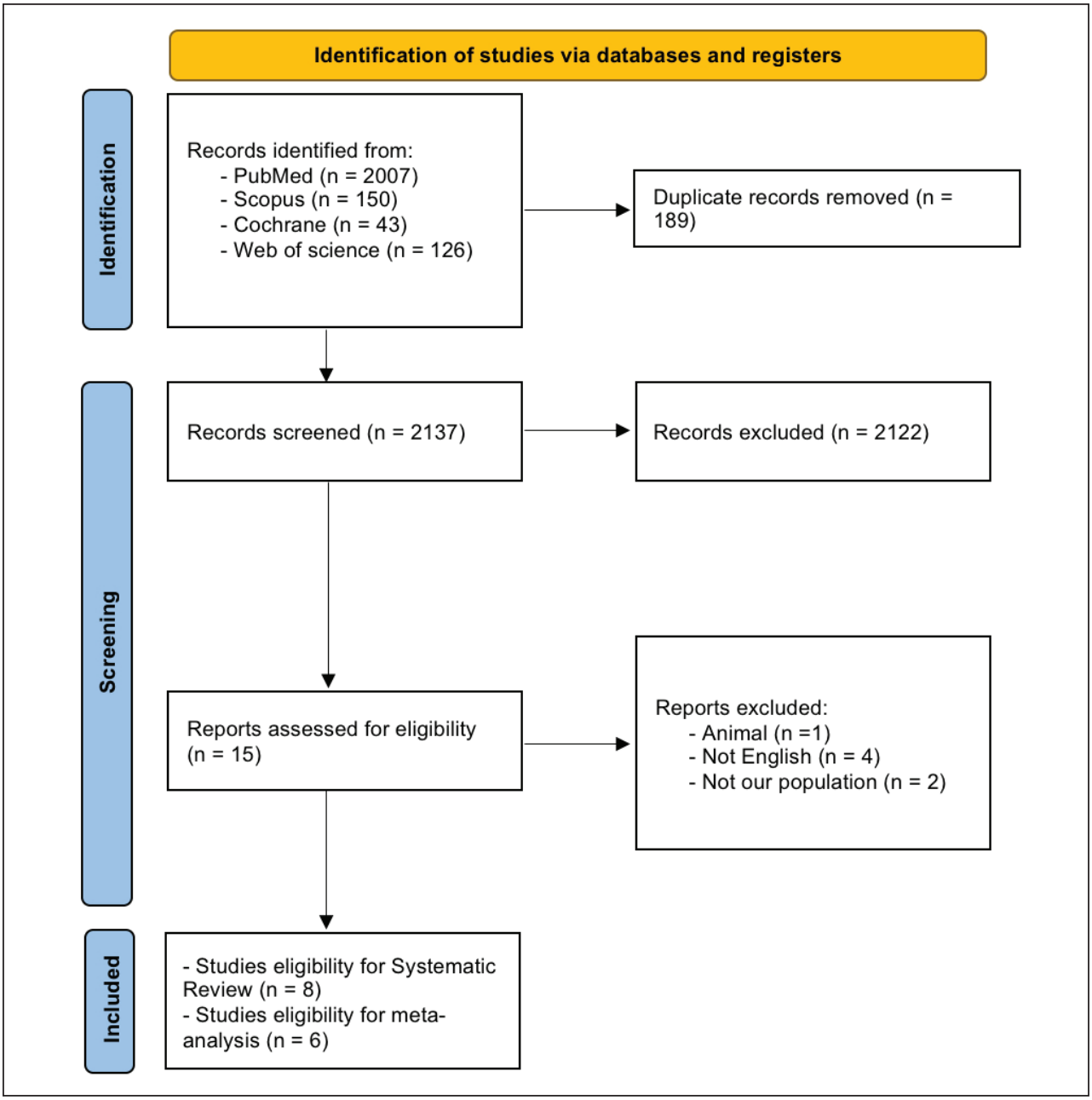


Figure 1. *PRISMA Flow diagram.*

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

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 dexketoprofen/thiamine + pyridoxine + cyanocobalamin vitamins demonstrated superior efficacy and a better safety profile compared with dexketoprofen 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 tablests × paracetamol 500 mg, Two tablests × ibuprofen 200 mg, Two tablests × 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 tablests × paracetamol 500 mg, Two tablests × ibuprofen 200 mg, Two tablests × 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	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. 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	1. The age of 30-60 years. 2. Diagnosis of primary knee osteoarthritis by an orthopedics (per descriptions, clinical symptoms, physical examinations, radiologic and relevant diagnostic criteria of this disease).	1. Pain intensity by VAS. 2. Western Ontario and McMaster Universities Osteoarthritis Index. 3. 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				

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

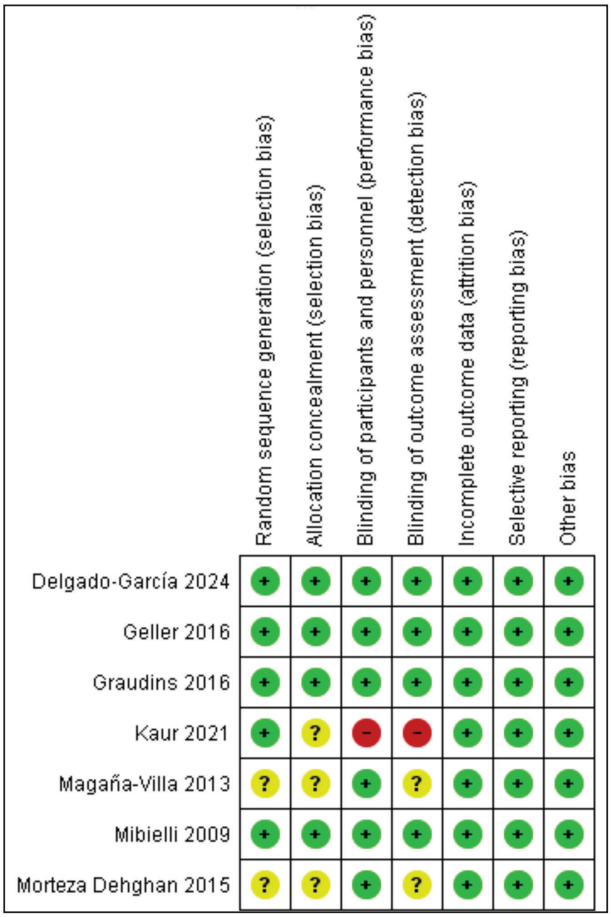


Figure 2. *Risk of bias summary of the included RCTs.*

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.

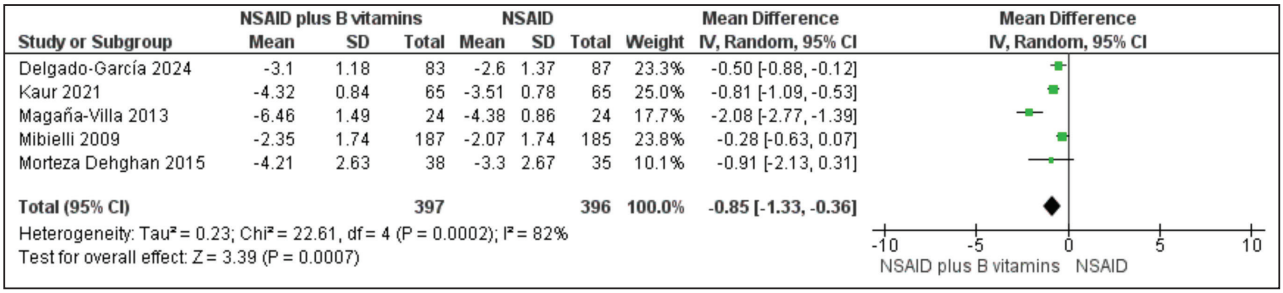


Figure 3. *Forest plot of pain by VAS score.*

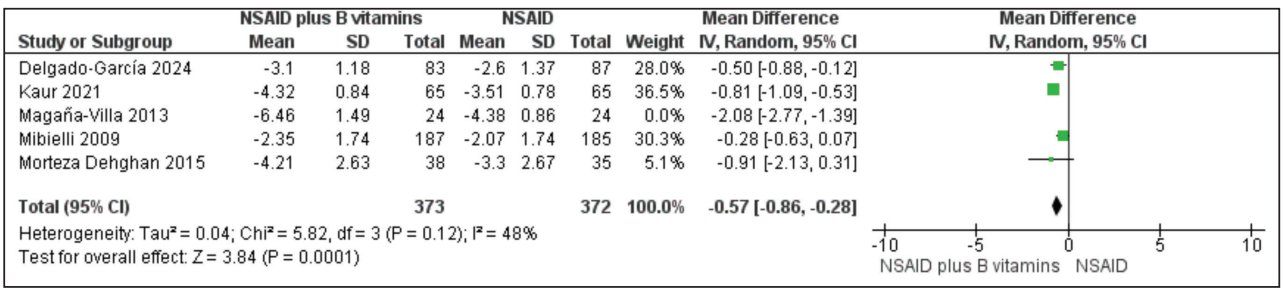


Figure 4. *Forest plot of pain by VAS score after excluding one study.*

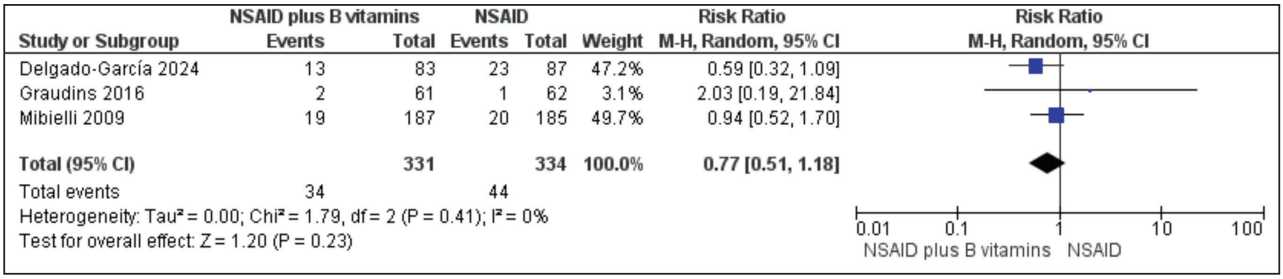


Figure 5. *Forest plot of adverse events incidence.*

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.

Acknowledgment
None.

List of Abbreviation
None.

Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

Funding
None.

Consent to participate
Not required.

Ethical approval
Not required.

Author details
Ibraheem Algarni[1], Ahmed A. Alfayez[2], Hussain A. Alharbi[3], Waleed K. Alsobhi[3], Abdulaziz A. Dhelemi[3], Malak N. AlShebel[4], Mousa M. Al anazi[5], Ziyad M. Alqurayqiri[6], Turki M. Alharbi[6]

1. Department of Family and Community Medicine, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
2. Department of Surgery, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
3. Medical Intern, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
4. College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
5. College of Medicine, Al Jouf University, Sakaka, Saudi Arabia
6. Medical Student, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

References

1. El-Tallawy SN, Nalamasu R, Salem GI, LeQuang JA, Pergolizzi JV, Christo PJ. Management of musculoskeletal pain: an update with emphasis on chronic musculoskeletal pain. Pain Theray. 2021;10(1):181–209. https://doi.org/10.1007/s40122-021-00235-2
2. Alghadir A, Anwer S. Prevalence of musculoskeletal pain in construction workers in Saudi Arabia. Sci World J. 2015;2015(1):529873. https://doi.org/10.1155/2015/529873
3. Dehghan L, Dalvand H, Samadi S, Monfared ME, Rafiei F. Prevalence of musculoskeletal pains among rehabilitation, dentistry and nursing students. J Arak Uni Med Sci. 2020;23(4):462–71. https://doi.org/10.32598/jams.23.4.2441.5.
4. Jin F, Guo Y, Wang Z, Badughaish A, Pan X, Zhang L, et al. The pathophysiological nature of sarcomeres in trigger points in patients with myofascial pain syndrome: a preliminary study. Eur J Pain. 2020;24(10):1968–78. https://doi.org/10.1002/ejp.1647
5. Aldhafian OR, Alsamari FA, Alshahrani NA, Alajmi MN, Alotaibi AM, Nwihadh NB, et al. Musculoskeletal pain among male faculty members of the College of Medicine and College of Dentistry. Medicine (Baltimore). 2021;100(21):e26176. https://doi.org/10.1097/MD.0000000000026176
6. Kamada M, Abe T, Kitayuguchi J. Until it hurts? Epidemiology of musculoskeletal pain in youth sports. J Phys Fit Sports Med. 2017;6(5):317–24. https://doi.org/10.7600/jpfsm.6.317
7. Kulkarni S, Adhikari S, Kumar KS, Mukkannavar P. Prevalence of musculoskeletal disorder among postmenopausal women: a cross sectional study. Indian J Physiother Occup. 2020;14(2):278–82. Available from: https://ijpot.com/scripts/IJPOT%20April-June_2020.pdf
8. Miranda VS, Decarvalho VB, Machado LA, Dias JM. Prevalence of chronic musculoskeletal disorders in elderly Brazilians: a systematic review of the literature. BMC Musculoskelet Disord. 2012;13(1):82. https://doi.org/10.1186/1471-2474-13-82
9. Wijnhoven HA, de Vet HC, Picavet HS. Prevalence of musculoskeletal disorders is systematically higher in women than in men. Clin J Pain. 2006;22(8):717–24. https://doi.org/10.1097/01.ajp.0000210912.95664.53
10. Puntillo F, Giglio M, Paladini A, Perchiazzi G, Viswanath O, Urits I, et al. Pathophysiology of musculoskeletal pain: a narrative review. Ther Adv Musculoskelet Dis. 2021;13:1759720X2199506. https://doi.org/10.1177/1759720X21995067
11. Moradi-Lakeh M, Forouzanfar MH, Vollset SE, El Bcheraoui C, Daoud F, Afshin A, et al. Burden of musculoskeletal disorders in the Eastern Mediterranean Region, 1990–2013: findings from the Global Burden of Disease Study 2013. Ann Rheum Dis. 2017;76(8):1365–73. https://doi.org/10.1136/annrheumdis-2016-210146
12. Safiri S, Kolahi AA, Cross M, Hill C, Smith E, Carson-Chahhoud K, et al. Prevalence, deaths, and disability-adjusted life years due to musculoskeletal disorders for 195 countries and territories 1990–2017. Arthritis Rheum. 2021;73(4):702–14. https://doi.org/10.1002/art.41571
13. Zhang G, Liu M, Chen H, Wu ZX, Gao YC, Ma Z, et al. NF-κB Signalling pathways in nucleus pulposus cell function and intervertebral disc degeneration. Cell Prolif. 2021;54(7):e13057. https://doi.org/10.1111/cpr.13057
14. Kim SJ, Jang HY, Lee SM. Effects of spinal mobilization with leg movement and neural mobilization on pain, mobility, and psychosocial functioning of patients with lumbar disc herniation: a randomized controlled study. Phys Ther Rehabil Sci. 2023;12(2):92–104. https://doi.org/10.14474/ptrs.2023.12.2.92
15. Chetty LA Retrospective evaluation of a knee rehabilitation class following evidence-based modifications. J Health Sci Res. 2022;8:7–10. https://doi.org/10.7324/jhsr.2023.812
16. Chu CR, Rodeo S, Bhutani N, Goodrich LR, Huard J, Irrgang J, et al. Optimizing clinical use of biologics in orthopaedic surgery: consensus recommendations from the 2018 AAOS/NIH U-13 conference. J Am Acad Orthop Surg. 2019;27(2):e50–63. https://doi.org/10.5435/JAAOS-D-18-00305
17. Homorogan C. The role of micrornas in osteoarthritis. Biomed J Sci Tech Res. 2022;41(5):33081–5. https://doi.org/10.26717/BJSTR.2022.41.006667
18. Shukla MK, Goyal M. Effect of maitland mobilization and conventional physiotherapy exercises in osteoarthritis knee: a comparative study. Int J Physiother Res. 2018;6(6):2952–6. https://doi.org/10.16965/ijpr.2018.193
19. Tieppo Francio V, Dima RS, Towery C, Davani S. Prolotherapy and low level laser therapy: a synergistic approach to pain management in chronic osteoarthritis. Anesth Pain Med. 2017;7(5):e14470. https://doi.org/10.5812/aapm.14470
20. Vyas R. Ergonomic assessment of prevalence of musculoskeletal disorders among indian agricultural

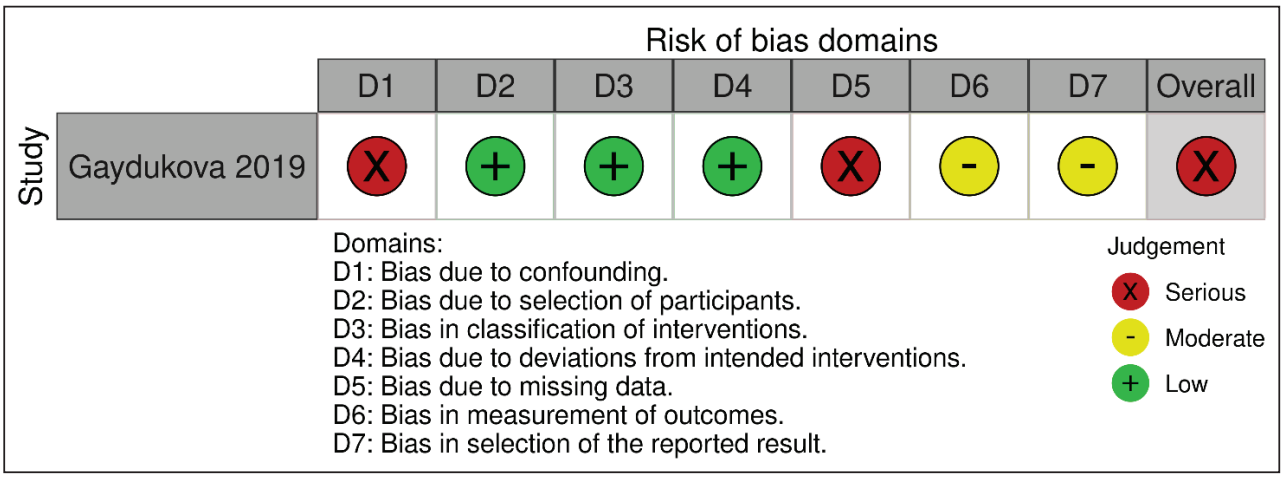
workers. J Ergon. 2015;(Special Issue 4):s4. https://doi.org/10.4172/2165-7556.S4-005

21. Mei F, Dong S, Li J, Xing D, Lin J. Preference of musculoskeletal pain treatment in middle-aged and elderly chinese people: a machine learning analysis of the China health and retirement longitudinal study. 2023;24:528. https://doi.org/10.1186/s12891-023-06665-7.
22. Li L, Xi Y, Wang Y, Gao Y, Lv X, Liu S, et al. Heat-stone massage for patients with chronic musculoskeletal pain: a protocol for multicenter randomized controlled trial. Front Med (Lausanne). 2023;10:1215858. https://doi.org/10.3389/fmed.2023.1215858
23. Marinho OD, Pereira A. Clinical efficacy and safety profile of topical etofenamate in the treatment of patients with musculoskeletal disorders: a systematic review. Pain Therapy. 2020;9(2):393–410. https://doi.org/10.1007/s40122-020-00177-1
24. Shi C, Ye Z, Shao Z, Fan B, Huang C, Zhang Y, et al. Multidisciplinary guidelines for the rational use of topical non-steroidal anti-inflammatory drugs for musculoskeletal pain (2022). J Clin Med. 2023;12(4):1544. https://doi.org/10.3390/jcm12041544
25. Tuskey A, Peura D. The use of H2 antagonists in treating and preventing NSAID-induced mucosal damage. Arthritis Res Ther. 2013;15(3):S6. https://doi.org/10.1186/ar4178
26. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. CNS Neurosci Ther. 2020;26(1):5–13. https://doi.org/10.1111/cns.13207
27. Caram-Salas NL, Reyes-García G, Medina-Santillán R, Granados-Soto V. Thiamine and cyanocobalamin relieve neuropathic pain in rats: synergy with dexamethasone. Pharmacology. 2006;77(2):53–62. https://doi.org/10.1159/000092643
28. Mortimer J, Lauman MK, Tan B, Dempsey CL, Shillington AC, Hutchins K. Pyridoxine treatment and prevention of hand-and-foot syndrome in patients receiving capecitabine. J Oncol Pharm Pract. 2003;9(4):161–6. https://doi.org/10.1191/1078155203jp116oa
29. Terán-Rosales F, Medina-Santillán R, Reyes-García G, Granados-Soto V. Synergistic antinociceptive interaction between acetaminophen or metamizol and B vitamins in the formalin test. Drug Dev Res. 2005;66(4):286–94. https://doi.org/10.1002/ddr.20071
30. Antonio C, Massimo T, Gianpaolo Z, Immacolata PM, Erika T. Oral high-dose thiamine improves the symptoms of chronic cluster headache. Case Rep Neurol Med. 2018;2018:3901619. https://doi.org/10.1155/2018/3901619
31. Randabunga EJ, Lukas E, Tumedia JL, Chalid SMT. Effect of pyridoxine on prostaglandin plasma level for primary dysmenorrheal treatment. Indones J Obstet Gynecol. 2018:239–42. https://doi.org/10.32771/inajog.v6i4.848
32. Wakeman M. An open-label pilot study to assess the effectiveness of krill oil with added vitamins and phytonutrients in the relief of symptoms of PMS. Nutr Diet Suppl. 2013;5:17–25. https://doi.org/10.2147/NDS.S48133
33. Dehghan M. Comparative effectiveness of B and E vitamins with diclofenac in reducing pain due to osteoarthritis of the knee. Arch Med. 2015;69(2):103–6. https://doi.org/10.5455/medarh.2015.69.103-106
34. Delgado-García P, Alcocer-Herrera JB, Urenda-Quezada A, Alonso-Martinez MD, Bautista-Mendoza MA, Romero-Antonio Y, et al. A randomized control trial of dexketoprofen/vitamin B (thiamine, pyridoxine and cyanocobalamin) fixed-dose combination in post-traumatic grade I-II cervical sprains. Clin Drug Investig. 2024;44(6):413–24. https://doi.org/10.1007/s40261-024-01370-2
35. Gaydukova I, Bichurina D, Popova YR, Rebrov A. Anti-inflammatory treatment in chronic back pain. Neurosci Behav Physiol. 2019;49(2):275–9. https://doi.org/10.1007/s11055-019-00726-y
36. Geller M, Mibielli MA, Nunes CP, da Fonseca AS, Goldberg SW, Oliveira L. Comparison of the action of diclofenac alone versus diclofenac plus B vitamins on mobility in patients with low back pain. J Drug Assess. 2016;5(1):1–3. https://doi.org/10.3109/21556660.2016.1163263
37. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
38. Higgins JP. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The cochrane collaboration, London, United Kingdom. 2008. Available from: http://www.cochrane-handbook.org
39. Oh KY. Validation of the Hanyang pain scale for clerical workers with musculoskeletal pain. J Pain Res. 2016;9:207–13. https://doi.org/10.2147/JPR.S102778
40. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
41. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomized trials. BMJ. 2019;366:4898. https://doi.org/10.1136/bmj.l4898
42. Graudins A, Meek R, Parkinson J, Egerton-Warburton D, Meyer A. A randomized controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury. Emerg Med Australas. 2016;28(6):666–72. https://doi.org/10.1111/1742-6723.12672
43. Kaur J, Rani S, Gulia A, Bhutani G, Kumar S, Narwat A. Role of vitamin B complex as an add-on therapy to diclofenac in patients with primary osteoarthritis of the knee. J Pharmacol Pharmacother. 2021;12(2):68–72. https://doi.org/10.4103/jpp.jpp_32_21
44. Magaña-Villa MC, Rocha-González HI, Fernández del Valle-Laisequilla C, Granados-Soto V, Rodríguez-Silverio J, Flores-Murrieta FJ, et al. B-vitamin mixture improves the analgesic effect of diclofenac in patients with osteoarthritis: a double blind study. Drug Research (Stuttg). 2013;63(6):289–92. https://doi.org/10.1055/s-0033-1334963
45. Mibielli MA, Geller M, Cohen JC, Goldberg SG, Cohen MT, Nunes CP, et al. Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study. Curr Med Res Opin. 2009;25(11):2589–99. https://doi.org/10.3111/13696990903246911
46. Wernham BG, Trumpatori B, Hash J, Lipsett J, Davidson G, Wackerow P, et al. Dose reduction of meloxicam in

dogs with osteoarthritis-associated pain and impaired mobility. J Vet Intern Med. 2011;25(6):1298–305. https://doi.org/10.1111/j.1939-1676.2011.00825.x

47. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021;375:n2321. https://doi.org/10.1136/bmj.n2321
48. Hunt RH, Lanas A, Stichtenoth DO, Scarpignato C. Myths and facts in the use of anti-inflammatory drugs. Ann Med. 2009;41(6):423–37. https://doi.org/10.1080/07853890902887295
49. Ruan J, Gong X, Kong J, Wang H, Zheng X, Chen T. Effect of B vitamin (folate, B6, and B12) supplementation on osteoporotic fracture and bone turnover markers: a meta-analysis. Med Sci Monit. 2015;21:875–81. https://doi.org/10.12659/MSM.893310
50. Pérez-Jimenez VR, Chumpitaz-Cerrate V, Chávez-Rimache L, Moreno-Villalobos DE, Rodríguez-Flores AA, Franco-Quino CI, et al. Synergistic anti-inflammatory effect of NSAIDs plus B vitamins administered pre and postoperatively in third molar surgery: randomized clinical trial. Braz Dent Sci. 2022;25(4):e3441. https://doi.org/10.4322/bds.2022.e3441

Supplementary Material



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