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Meta-Analysis

Comparing the incidence of adverse events following topical versus oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: a systematic review and meta-analysis

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ABSTRACT

Knee osteoarthritis is a prevalent condition that significantly impairs the quality of life, often managed with non-steroidal anti-inflammatory drugs (NSAIDs). While oral NSAIDs are widely used for their systemic effects, they are associated with a higher risk of adverse events (AEs). Topical NSAIDs offer localized approach with potentially fewer systemic side effects, making them an alternative. This meta-analysis compared the incidence of overall AEs associated with topical versus oral NSAIDs in patients with knee osteoarthritis. A systematic search was conducted in PubMed, Cochrane Library, and Embase for studies comparing AEs in patients with knee osteoarthritis treated with topical versus oral NSAIDs. Eight studies with a total of 2,181 participants were included. The pooled odds ratio (OR) for overall AEs was calculated, and heterogeneity among studies was assessed using I^2 statistic. Publication bias was evaluated using a funnel plot. The meta-analysis demonstrated that topical NSAIDs were associated with lower incidence of AEs compared to oral NSAIDs, with a pooled OR of 0.62 (95% CI: 0.38 to 1.00). This suggests that patients treated with topical NSAIDs were 38% less likely to experience AEs than those treated with oral NSAIDs (p=0.05). Significant heterogeneity was observed among the studies (I^2=80%). The funnel plot indicated potential publication bias. Topical NSAIDs offer safer alternative to oral NSAIDs for managing knee osteoarthritis, particularly in reducing the risk of AEs. While the findings are promising, the high degree of heterogeneity and potential publication bias underscore the need for further research to confirm these results.

Keywords: Knee osteoarthritis, NSAIDs, Topical NSAIDs, Oral NSAIDs, Adverse events, Meta-analysis

INTRODUCTION

Knee osteoarthritis is a prevalent degenerative joint disease that significantly impacts the quality of life, especially in older adults. Characterized by the progressive deterioration of articular cartilage, osteoarthritis leads to pain, stiffness, and functional limitations, ultimately resulting in disability.[1,2] As one of the most common forms of arthritis, knee osteoarthritis poses a substantial burden on healthcare systems worldwide due to its chronic nature and the increasing prevalence associated with an aging population.[3]

The pathophysiology of knee osteoarthritis involves a complex interplay between mechanical, biological, and biochemical factors. These processes contribute to the

degradation of cartilage, alterations in subchondral bone, and inflammation of the synovium.[2,3] Pain, the primary symptom of knee osteoarthritis, arises from a combination of these structural changes and the sensitization of nociceptive pathways. The management of pain is, therefore, a critical aspect of osteoarthritis treatment, aiming to improve function and quality of life while slowing the progression of the disease.[3,4]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications for the management of pain and inflammation in knee osteoarthritis. NSAIDs exert their effects by inhibiting the cyclooxygenase (COX) enzymes, particularly COX-2, which are involved in the synthesis of prostaglandins—lipid compounds that play a key role in pain and inflammation.[5] By reducing the production of prostaglandins, NSAIDs help to alleviate the symptoms of osteoarthritis, making them a cornerstone of pharmacologic treatment.[5,6]

NSAIDs are available in both oral and topical formulations, each with distinct pharmacokinetic properties and safety profiles. Oral NSAIDs, which are absorbed systemically, are widely used due to their convenience and effectiveness.[1,6] However, their systemic absorption is associated with a range of adverse events (AEs), particularly gastrointestinal complications such as ulcers, bleeding, and perforation. The risk of these AEs increases with the duration of use and the dosage, making long-term management with oral NSAIDs a challenge, especially in elderly patients who may have comorbid conditions or be taking other medications that further elevate the risk.[6,7]

In contrast, topical NSAIDs are applied directly to the skin over the affected joint, allowing for local drug delivery with minimal systemic absorption. This localized application is intended to provide effective pain relief while reducing the risk of systemic AEs associated with oral NSAIDs. Several topical NSAIDs, such as diclofenac, ibuprofen, and ketoprofen, have been formulated into gels, creams, and patches for the treatment of knee osteoarthritis. These formulations are designed to penetrate the skin and deliver the active drug to the underlying tissues, including the synovium and cartilage.[8,9]

The efficacy of topical NSAIDs in managing knee osteoarthritis pain has been demonstrated in numerous clinical trials, with several studies showing comparable pain relief to oral NSAIDs. However, the safety profile of topical NSAIDs remains a subject of ongoing investigation. While the risk of systemic AEs is generally lower with topical administration, there is still the potential for local AEs such as skin irritation, dermatitis, and hypersensitivity reactions.[9,10] Moreover, the comparative risk of systemic AEs between topical and oral NSAIDs is a critical consideration for clinicians when choosing the appropriate treatment modality for individual patients.[9,11]

Given the widespread use of NSAIDs and the potential for AEs, there is a growing interest in understanding the relative safety of topical versus oral formulations in the treatment of knee osteoarthritis. This is particularly relevant in the context of an aging population, where the burden of knee osteoarthritis is expected to rise, and where the management of AEs becomes increasingly important due to polypharmacy and age-related physiological changes.[10,12]

Despite the availability of numerous studies comparing the safety of topical and oral NSAIDs, the evidence remains fragmented, with varying results depending on the study design, patient population, and specific NSAID formulations used. Some studies suggest a significantly lower risk of systemic AEs with topical NSAIDs, while others report similar or even greater risks compared to oral formulations. The variability in findings may be attributed to differences in study methodologies, including the duration of treatment, the specific AEs monitored, and the criteria used for diagnosing and reporting these events. This meta-analysis aims to systematically evaluate and compare the incidence of adverse events associated with topical versus oral NSAIDs in the treatment of knee osteoarthritis.

METHODS

Study design and objectives

This meta-analysis was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to systematically evaluate and compare the incidence of adverse events (AEs) between topical and oral NSAIDs in patients with knee osteoarthritis.[13] The primary objective was to synthesize available evidence on the safety profiles of topical versus oral NSAIDs, focusing on the overall incidence of AEs. Secondary objectives included examining specific types of AEs and assessing the consistency of the findings across different studies. This meta-analysis was conducted during the period from March 2024 to September 2024.

Literature search strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed, the Cochrane Library, Web of Science, Medline, Scopus, and Google Scholar. The search strategy was designed to identify all relevant studies published up to August 2024, without any language or publication date restrictions. Keywords and medical subject headings (MeSH) terms related to "knee osteoarthritis," "NSAIDs," "topical," "oral," and "adverse events" were used to capture a broad range of studies.

The search strategy was refined using Boolean operators, and the results were supplemented by manually screening the reference lists of relevant articles to ensure a comprehensive inclusion of studies.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: randomized controlled trials (RCTs) or observational studies comparing the incidence of AEs in patients with knee osteoarthritis treated with either topical or oral NSAIDs; studies involving adult participants diagnosed with knee osteoarthritis based on established clinical criteria; studies that reported sufficient data to calculate the odds ratio (OR) and 95% confidence intervals (CIs) for AEs; and studies published in peer-reviewed journals in the last 20 years. Exclusion criteria included studies that did not directly compare topical versus oral NSAIDs, those that lacked adequate data for meta-analysis, and non-peer-reviewed sources such as conference abstracts and commentaries.

Study selection and data extraction

The study selection process involved two independent reviewers who screened titles and abstracts of all identified records. Full-text articles were retrieved for studies that met the initial screening criteria. Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer. The data extraction process was standardized using a pre-piloted data extraction form to ensure consistency and accuracy. The extracted data included study characteristics (authors, publication year, country, study duration, sample size), patient demographics (age, sex), intervention details (type and dosage of NSAID, route of administration), duration of follow-up, and outcomes (number of AEs in both topical and oral NSAID groups).

Data synthesis and statistical analysis

A quantitative synthesis was performed using a random-effects model to account for variability among studies. The primary outcome was the overall incidence of AEs, which was pooled using the Mantel-Haenszel method to calculate the OR and 95% CI. The inverse variance method was applied to weight studies according to the precision of their estimates. Heterogeneity among studies was evaluated using the Chi-square test and the I^2 statistic, with I^2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Sensitivity analyses were conducted to explore the robustness of the findings by excluding studies with a high risk of bias or those with extreme effect sizes. Publication bias was assessed using funnel plots, which plot the effect size against the standard error of each study. An asymmetrical distribution of studies in the funnel plot suggests potential publication bias.

The results of the meta-analysis were reported according to PRISMA guidelines. Pooled ORs with 95% CIs were presented for the primary outcome, along with forest plots to visually represent the effect sizes of individual studies. The findings were interpreted in the context of the quality and heterogeneity of the included studies. The clinical significance of the results was discussed, with a focus on the implications for the safety and management of knee osteoarthritis using topical versus oral NSAIDs.

RESULTS

The comprehensive literature search yielded a total of 872 records from various databases, including PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar. After removing 406 duplicates, 466 unique records were identified for the title and abstract screening phase. Of these, 417 studies were excluded based on irrelevance to the study criteria, leaving 49 studies for full-text assessment. All 49 full-text articles were successfully retrieved and evaluated for eligibility. However, 41 studies were excluded due to reasons such as insufficient data on adverse events or inappropriate study design. Consequently, 8 studies met the inclusion criteria and were included in the final quantitative synthesis, as illustrated in the PRISMA flow diagram (Figure 1).

Characteristics and findings of the included studies

Table 1 summarizes the characteristic of the included studies. The eight included studies spanned several countries, including Canada, Germany, the United Kingdom, the United States, China, and India, reflecting a diverse geographical representation. The study durations varied, with most studies conducted between 2001 and 2015. For instance, the study by Tugwell et al was conducted in Canada from 2001 to 2002, while the study by Shinde et al took place in India from 2014 to 2015.[14,21] The sample sizes for the topical and oral NSAID groups were generally well-balanced, ranging from small samples, such as nine and ten participants in Tiso et al, to larger cohorts like 311 participants per group in Tugwell et al.[14,18]

The age of participants varied across the studies, with the mean age ranging from mid-40s to late 60s. The youngest group was observed in Shinde et al, where the mean age was approximately 46.5 years in the topical group and 43.0 years in the oral group.[21] Conversely, Underwood et al reported the oldest cohort, with mean ages of 68 and 63 years for the topical and oral groups, respectively.[16] The gender distribution was also reported, with males comprising between 0% to 68% of the topical groups across the studies. Notably, the study by Tiso et al included no male participants in the topical group, whereas the highest male percentage was observed in Shinde et al with 68%.[18,21]

The interventions included a variety of NSAID formulations, both topical and oral. Commonly used topical interventions included diclofenac solution, ketoprofen in Transferosome gel, and loxoprofen sodium patches, while oral interventions frequently involved diclofenac tablets, celecoxib, and ibuprofen. The duration of follow-up ranged from as short as two weeks in Tiso et al to as long as 96 weeks in Underwood et al, indicating a wide variation in the observation periods across

studies.[16,18] The prevalence of AEs differed significantly between the topical and oral groups. For example, Tugwell et al reported a 4.2% prevalence of AEs in the topical group compared to 20.9% in the oral group, while Underwood et al observed nearly identical rates of AEs between the two groups (55.8% and 55.6%, respectively) (Table 1).[14,16]

Quantitative data synthesis

The meta-analysis comparing the incidence of overall adverse events between topical and oral NSAID groups revealed a significant trend favoring the topical formulations. Across the eight included studies, the total number of adverse events in the topical group was 372 out of 1091 participants, while the oral group experienced 449 adverse events out of 1090 participants. The pooled odds ratio (OR) was 0.62 (95% CI: 0.38 to 1.00), suggesting that participants receiving topical NSAIDs were 38% less likely to experience adverse events compared to those receiving oral NSAIDs. This finding approached statistical significance with a Z-value of 1.94 and a p value of 0.05. (Figure 2).

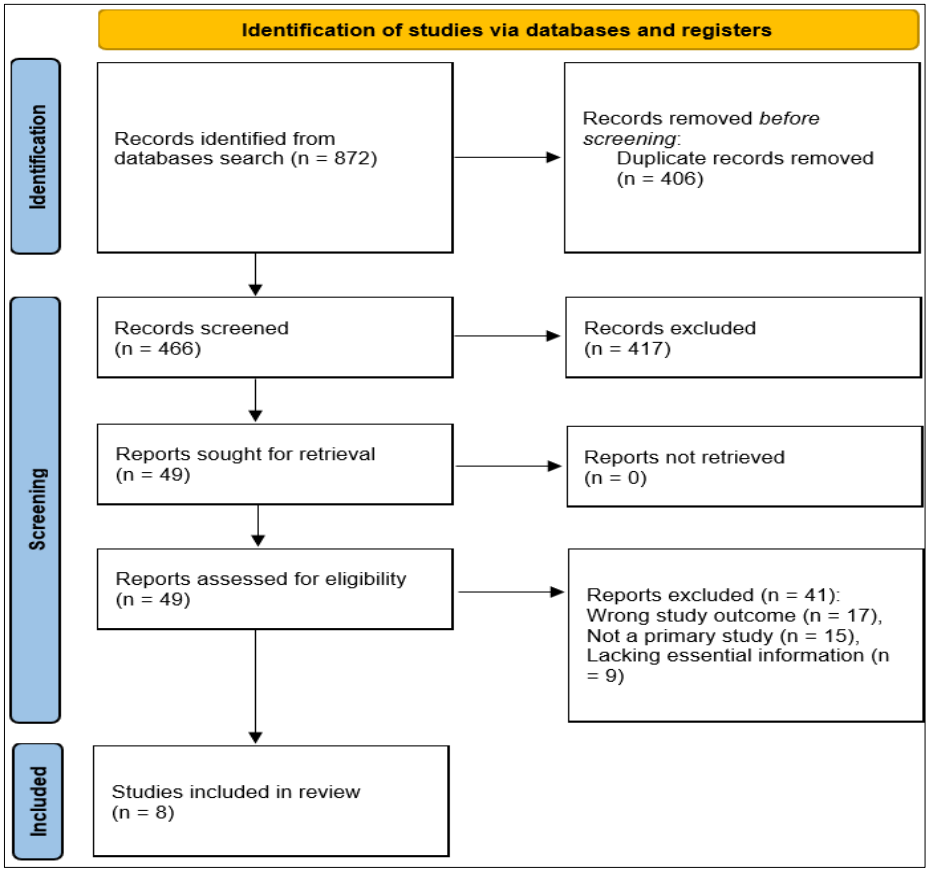

Figure 1: PRISMA flow diagram for summary of study search and screening processes.

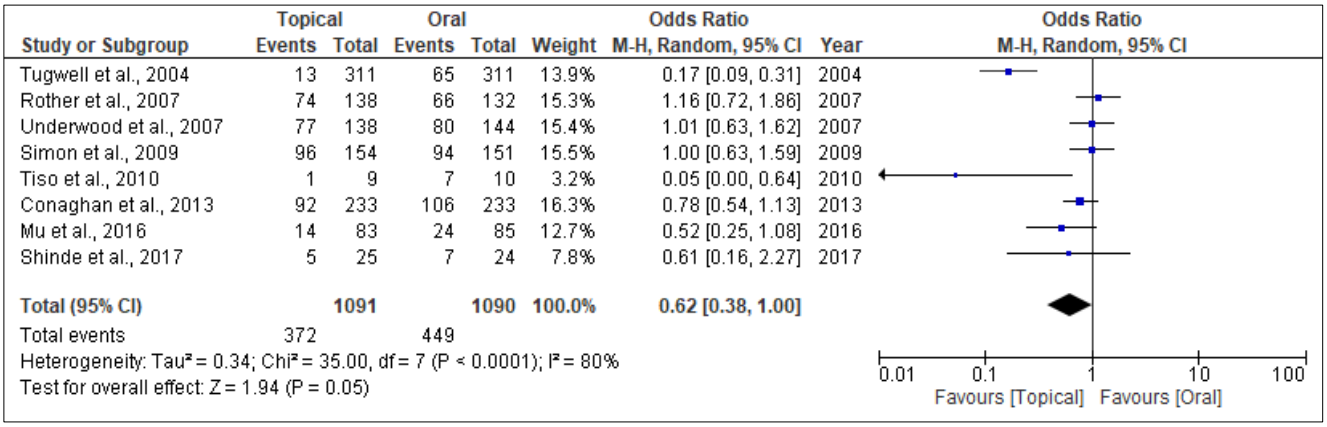

Figure 2: Forest plot of comparing overall adverse events among topical versus oral NSAIDs groups in patients with knee osteoarthritis.

Table 1: Characters and findings of the included studies (n=8).

Study	Country	Study duration	Intervention (T)	Intervention (O)	Sample size (T)	Sample size (O)	Age (T)	Age (O)	Male % (T)	Male % (O)	Follow up duration (weeks)	Prevalence of all AEs (T) (%)	Prevalence of all AEs (O) (%)
Tugwell et al, 2004[14]	Canada	2001-2002	Diclofenac solution 1.5% (50 drops)	150 mg diclofenac capsules	311	311	64± 10	63± 10	43	43	12	4.2	20.9
Rother et al, 2007[15]	Germany	2003	110 mg ketoprofen in 4.8 g transferosome + oral placebo	100 mg oral celecoxib + placebo gel	138	132	63.3 ±10.1	62.4 ±9.6	45.7	37.9	6	53.6	50.0
Underwood et al, 2007[16]	UK	2003-2006	Ibuprofen 1.5 g/day	Ibuprofen 1.2 g/day	138	144	68	63	49	44	96	55.8	55.6
Simon et al, 2009[17]	Canada	2004-2005	Diclofenac solution 1.5% (40 drops) four times daily + oral placebo	100 mg diclofenac tablets + topical placebo solution	154	151	61.7 ±9.8	62.0 ±10.5	32.5	37.1	12	62.3	62.3
Tiso et al, 2010[18]	USA	2008	Topical 4% ibuprofen gel	Ibuprofen tablets	9	10	58.9 ±10.3	57.0 ±7.9	0.0	20	2	11.1	70.0
Conaghan et al, 2013[19]	UK, Czech Republic, Germany, Poland	2008-2009	Ketoprofen 50 mg in 2.2 g transferosome	100 mg oral celecoxib	233	233	61.6 (37–85)	62.0 (38–90)	44.2	33.1	12	39.5	45.5
Mu et al, 2016[20]	China	2010-2011	Loxoprofen sodium 100 mg patches	Loxoprofen sodium 60 mg tablets	83	85	57.3 ±9.6	56.9 ±9.0	23.5	19.3	4	16.9	28.2
Shinde et al, 2017[21]	India	2014 - 2015	Transdermal diclofenac diethylamine patch 100 mg once daily	Tablet diclofenac sodium SR 100 mg once daily	25	24	46.5 ±12.0	43.0 ±13.4	68.0	58.3	4	20.0	29.2

T: Topical NSAID group, O: Oral NSAID group

The contribution of individual studies to this overall effect varied. Tugwell et al demonstrated a particularly strong protective effect of topical NSAIDs, with an OR of 0.17 (95% CI: 0.09 to 0.31), significantly reducing the risk of adverse events compared to the oral group.[14] On the other hand, studies like Rother et al and Simon et al showed ORs close to 1, indicating similar rates of adverse events between the two groups.[15,17] The high degree of heterogeneity among the studies, as evidenced by an I^2 of 80% and a Tau^2 of 0.34, underscores the variability in study outcomes, which could be attributed to differences in study designs, populations, and interventions.

Publication bias

The funnel plot for assessing publication bias (Figure 3) revealed an asymmetrical distribution of studies, which may indicate the presence of publication bias. This

asymmetry suggests that smaller studies with non-significant or negative results may have been underrepresented in the literature, potentially leading to an overestimation of the protective effect of topical NSAIDs in the meta-analysis. The possibility of publication bias necessitates a cautious interpretation of the results, acknowledging that the true effect size may be less pronounced than the pooled estimate suggests.

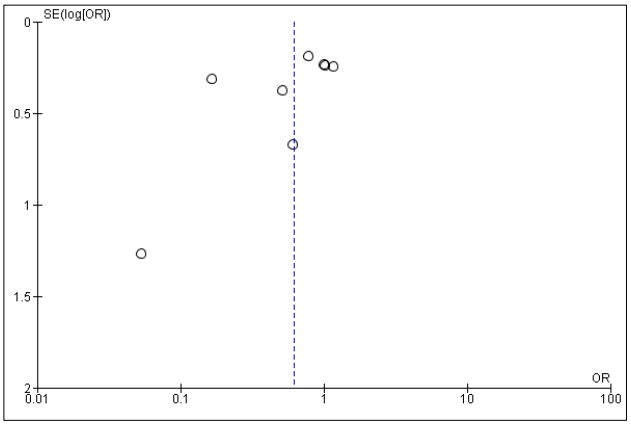

Figure 3: Funnel plot for assessment of publication bias.

DISCUSSION

NSAIDs are commonly prescribed for managing pain and inflammation associated with knee osteoarthritis, a prevalent condition that significantly impacts the quality of life for millions of people worldwide.[5,8] Both oral and topical NSAIDs are widely used, with the former being more prevalent due to its systemic effects and perceived potency. However, the systemic absorption of oral NSAIDs increases the risk of AEs, particularly gastrointestinal, cardiovascular, and renal complications. Topical NSAIDs, on the other hand, offer a targeted approach with potentially fewer systemic side effects, making them an attractive alternative, especially for long-term use.[9,11] This meta-analysis was conducted to compare the incidence of AEs associated with topical versus oral NSAIDs in patients with knee osteoarthritis, aiming to provide a comprehensive synthesis of the evidence to guide clinical decision-making.

Our meta-analysis included eight studies with a total of 2,181 participants, comparing the incidence of overall AEs between topical and oral NSAIDs in patients with knee osteoarthritis. The pooled odds ratio (OR) for overall AEs favored the topical NSAIDs, with an OR of 0.62 (95% CI: 0.38 to 1.00). This indicates that patients receiving topical NSAIDs were 38% less likely to experience AEs compared to those receiving oral NSAIDs, a finding that approached statistical significance (Z=1.94, p=0.05). The studies included in the analysis varied in terms of sample sizes, interventions, and follow-up durations, contributing to a high degree of heterogeneity (I^2=80%). Despite this variability, the overall trend suggests a potential safety advantage for topical NSAIDs over their oral counterparts in the management of knee osteoarthritis.

The results of this meta-analysis underscore the potential safety benefits of topical NSAIDs over oral NSAIDs in reducing the incidence of AEs in patients with knee osteoarthritis. The pooled OR of 0.62 indicates a substantial reduction in the risk of AEs with topical formulations, which is consistent with the pharmacokinetic profiles of these drugs. Topical NSAIDs are designed to provide localized pain relief with minimal systemic absorption, thereby reducing the likelihood of systemic side effects. This is particularly important for populations at higher risk of NSAID-related complications, such as the elderly or those with pre-existing gastrointestinal or cardiovascular conditions.[10,11]

The individual studies included in this meta-analysis provide further insight into the comparative safety profiles of topical and oral NSAIDs. For example, Tugwell et al reported a significantly lower incidence of AEs in the topical NSAID group compared to the oral group, with an OR of 0.17 (95% CI: 0.09 to 0.31).[14] This study, conducted in Canada, included a large sample size of 311 participants per group and demonstrated a clear safety advantage for topical diclofenac over oral diclofenac capsules. The findings from this study are particularly compelling given the similar sample sizes and demographic characteristics between the groups, which reduce the potential for confounding factors.

In contrast, other studies, such as Rother et al and Simon et al, reported ORs closer to 1, indicating no significant difference in the incidence of AEs between topical and oral NSAIDs.[15,17] Rother et al conducted a study in Germany comparing ketoprofen in Transferosome gel to oral celecoxib, while Simon et al examined the effects of topical versus oral diclofenac in a Canadian cohort.[15,17] The findings from these studies suggest that the safety advantage of topical NSAIDs may not be universally applicable across all formulations and patient populations. It is possible that factors such as the specific drug formulation, the severity of osteoarthritis, and patient adherence to the treatment regimen may influence the comparative safety profiles of topical and oral NSAIDs.

The heterogeneity observed in this meta-analysis (I^2=80%) indicates substantial variability in the study outcomes, which may be attributed to differences in study design, patient populations, and intervention protocols. For instance, the duration of follow-up varied significantly across the included studies, ranging from as short as 2 weeks in Tiso et al to as long as 96 weeks in Underwood et al.[16,18] Longer follow-up periods may provide a more accurate assessment of the long-term safety profiles of NSAIDs, particularly for chronic conditions such as knee osteoarthritis. The variation in follow-up durations may partially explain the differences in AE rates observed across the studies.

The potential for publication bias, as suggested by the asymmetry in the funnel plot, is an important consideration in interpreting the findings of this meta-analysis. In the context of this meta-analysis, the possibility of publication bias suggests that the true difference in AE rates between topical and oral NSAIDs may be smaller than our pooled estimate indicates. To address this limitation, future systematic reviews should employ strategies such as trial registries and comprehensive search strategies to capture all relevant studies, including unpublished data.[22,23]

It is important to recognize the limitations of our meta-analysis. The high degree of heterogeneity among the included studies limits the generalizability of the findings, and the potential for publication bias further complicates the interpretation of the results. Additionally, the relatively small number of studies included in the analysis (n=8) reduces the statistical power to detect differences between the groups, particularly for rare AEs. Despite these limitations, the overall trend favoring topical NSAIDs is robust and aligns with the broader literature on the comparative safety of these drugs.

The findings of this meta-analysis have important implications for clinical practice, particularly in the management of knee osteoarthritis in populations at risk for NSAID-related AEs. The demonstrated safety advantage of topical NSAIDs suggests that they should be considered as a first-line treatment option for patients who require long-term NSAID therapy but are at risk for systemic complications. This is particularly relevant for elderly patients, those with a history of gastrointestinal bleeding or cardiovascular disease, and patients who require concurrent use of other medications that may increase the risk of NSAID-related AEs.

However, the choice between topical and oral NSAIDs should also consider other factors, such as the severity of osteoarthritis symptoms, patient preferences, and the cost and availability of topical formulations. In cases where systemic pain relief is necessary, oral NSAIDs may still be appropriate, but their use should be accompanied by strategies to mitigate the risk of AEs, such as the co-prescription of proton pump inhibitors for gastrointestinal protection or regular monitoring of renal function.

Limitations

Given the limitations of the current evidence base, future research should focus on large-scale, high-quality randomized controlled trials that directly compare the safety and efficacy of topical versus oral NSAIDs in diverse patient populations. These studies should aim to standardize the reporting of AEs, including both overall and specific types of events, to facilitate more accurate comparisons across studies. Additionally, future meta-analyses should employ advanced statistical techniques, such as network meta-analysis or Bayesian hierarchical modelling, to account for heterogeneity and potential publication bias.

CONCLUSION

In conclusion, this meta-analysis provides evidence that topical NSAIDs are associated with a lower incidence of AEs compared to oral NSAIDs in patients with knee osteoarthritis, with a pooled OR of 0.62 (95% CI: 0.38 to 1.00). While the findings suggest a potential safety advantage for topical NSAIDs, the high degree of heterogeneity and potential publication bias highlight the need for further research to confirm these results.

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REFERENCES

1. Sharma L. Osteoarthritis of the knee. N Engl J Med. 2021;384(1):51-9.
2. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. JAMA. 2021;325(6):568-78.
3. Primorac D, Molnar V, Rod E, Jeleč Ž, Čukelj F, Matišić V, et al. Knee osteoarthritis: a review of pathogenesis and state-of-the-art non-operative therapeutic considerations. Genes. 2020;11(8):854.
4. Driban JB, Harkey MS, Barbe MF, Ward RJ, MacKay JW, Davis JE, et al. Risk factors and the natural history of accelerated knee osteoarthritis: a narrative review. BMC Musculoskelet Disord. 2020;21:1.
5. Horecka A, Hordyjewska A, Blicharski T, Kurzepa J. Osteoarthritis of the knee—Biochemical aspect of applied therapies: A review. Bosnian J Basic Med Sci. 2022;22(4):488.
6. Magni A, Agostoni P, Bonezzi C, Massazza G, Menè P, Savarino V, et al. Management of osteoarthritis: expert opinion on NSAIDs. Pain Ther. 2021;10(2):783-808.
7. Vincent TL. Peripheral pain mechanisms in osteoarthritis. Pain. 2020;161:S138-46.
8. Bariguian Revel F, Fayet M, Hagen M. Topical diclofenac, an efficacious treatment for osteoarthritis: a narrative review. Rheumatol Ther. 2020;7(2):217-36.
9. Richard MJ, Driban JB, McAlindon TE. Pharmaceutical treatment of osteoarthritis. Osteoarthr Cartil. 2023;31(4):458-66.
10. Richard MJ, Driban JB, McAlindon TE. Pharmaceutical treatment of osteoarthritis. Osteoarthr Cartil. 2023;31(4):458-66.
11. Lee JK, Abbas AA, Cheah TE, Simanjuntak RN, Sockalingam S, Roohi S. Topical nonsteroidal anti-inflammatory drugs for management of osteoarthritis

pain: A consensus recommendation. J Orthop Res. 2023;41(9):1916-24.
12. Cao P, Li Y, Tang Y, Ding C, Hunter DJ. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. Exp Opinion Pharmacother. 2020;21(7):797-809.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021;134:103-12.
14. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. J Rheumatol. 2004;31(10):2002-12.
15. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. Ann Rheum Dis. 2007;66(9):1178-83.
16. Underwood M, Ashby D, Cross P, Hennessy E, Letley L, Martin J, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ. 2008;336(7636):138-42.
17. Simon LS, Grierson LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. Pain. 2009;143(3):238-45.
18. Tiso RL, Tong-Ngork S, Fredlund KL. Oral versus topical Ibuprofen for chronic knee pain: a prospective randomized pilot study. Pain Physician. 2010;13(5):457.
19. Conaghan PG, Dickson J, Bolten W, Cevc G, Rother M. A multicentre, randomized, placebo- and active-controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome gel (IDEA-033) with ketoprofen-free vehicle (TDT 064) and oral celecoxib for knee pain associated with osteoarthritis. Rheumatology (Oxford). 2013;52(7):1303-12.
20. Mu R, Bao CD, Chen ZW, Zheng Y, Wang GC, Zhao DB, et al. Efficacy and safety of loxoprofen hydrogel patch versus loxoprofen tablet in patients with knee osteoarthritis: a randomized controlled non-inferiority trial. Clin Rheumatol. 2016;35:165-73.
21. Shinde VA, Kalikar M, Jagtap S, Dakhale GN, Bankar M, Bajait CS, et al. Efficacy and safety of oral diclofenac sustained release versus transdermal diclofenac patch in chronic musculoskeletal pain: a randomized, open label trial. J Pharmacol Pharmacother. 2017;8(4):166-71.
22. Page MJ, Sterne JA, Higgins JP, Egger M. Investigating and dealing with publication bias and other reporting biases in meta-analyses of health research: A review. Res Synthesis Method. 2021;12(2):248-59.
23. Doleman B, Freeman SC, Lund JN, Williams JP, Sutton AJ. Funnel plots may show asymmetry in the absence of publication bias with continuous outcomes dependent on baseline risk: presentation of a new publication bias test. Res Synthesis Method. 2020;11(4):522-34.

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