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Efficacy and safety of different topical diclofenac formulations for the treatment of knee osteoarthritis: a meta-analysis of short-term and long-term treatment comparisons

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Abstract

Objective This meta-analysis evaluates the efficacy and safety of various topical dosage forms of diclofenac (gel, solution, and patch) for the treatment of knee osteoarthritis.

Methods A comprehensive literature search was conducted in PubMed, Embase, Cochrane Library, and Web of Science for randomized controlled trials evaluating topical diclofenac formulations in knee osteoarthritis patients. Data on pain relief, functional outcomes, and adverse events were extracted. The primary outcomes were pain and function scores at different follow-up intervals (1–2 weeks, 3–6 weeks, 8–12 weeks), and safety outcomes.

Results A total of 12 randomized controlled trials (RCTs) were included in the analysis. Diclofenac gel, solution, and patch were all shown to significantly alleviate pain and improve function in patients with knee osteoarthritis. At 1–2 weeks, the diclofenac patch delivered the most pronounced short-term pain relief (SMD: -0.64; 95% CI: -0.90 to -0.39), while the gel and solution demonstrated sustained efficacy over the mid-term (3–6 weeks) and long-term (8–12 weeks). whereas skin-related adverse events, systemic side effects and withdrawal rates remained low across all formulations. The overall quality of evidence was assessed as moderate to high, reinforcing the robustness of the findings.

Conclusions Topical diclofenac formulations (gel, solution, patch) significantly improve pain and function in knee osteoarthritis compared to placebo. All formulations were well-tolerated, with no significant increase in adverse events. These findings support the use of topical diclofenac for short-term pain relief and functional improvement in KOA patients.

Keywords Topical diclofenac, Osteoarthritis, Knee, Pain, Physical function, Adverse events

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Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease, characterized by progressive loss of articular cartilage, subchondral bone remodeling, synovitis, and osteophyte formation, leading to joint pain, stiffness, and functional impairment [1, 2]. OA typically affects weight-bearing joints like the knees and hips, significantly reducing patients' quality of life, and imposing a heavy burden on global healthcare systems [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat OA due to their effectiveness in reducing pain and inflammation [4–6]. Diclofenac sodium, a commonly used NSAID, works by inhibiting cyclooxygenase (COX) enzymes, which are crucial in prostaglandin synthesis and inflammatory responses [7–10]. Although systemic NSAIDs, like oral diclofenac, are effective treatments, long-term use may increase the risk of gastrointestinal, cardiovascular, and renal adverse effects. Consequently, topical NSAID formulations are gaining popularity as they they deliver local concentrations of drug, reducing systemic absorption and minimizing the risk of systemic side effects [11–14]. Topical diclofenac is available in various dosage forms, including gels, solutions, and patches, and is commonly used to alleviate localized joint pain in OA patients. These topical formulations effectively relieve pain and improve joint function by delivering the drug directly to the site of pain and disability, minimizing the adverse effects associated with oral medications [14]. In particular, it remains uncertain whether variations in therapeutic efficacy or the incidence of adverse events (AEs) exist among different pharmaceutical dosage forms, such as gels and solutions.

In the existing randomized controlled trials (RCTs), the primary pharmaceutical dosage forms studied predominantly include solutions, gels, and patches [15–27]. Given the widespread application of these dosage forms in clinical practice and the robust supporting research data, it is crucial to assess their efficacy and safety in patients with knee Osteoarthritis (KOA), integrate evidence, and provide clearer clinical guidance. This meta-analysis aims to compare the efficacy and safety of the aforementioned three dosage forms of diclofenac sodium in treating KOA, with a particular focus on the results of randomized controlled trials. By analyzing data on pain relief, functional improvement, and AEs, this study aims to identify whether one of the formulations presents a lower risk profile while effectively managing KOA symptoms.

Methods

The study protocol has been registered with PROSPERO (CRD42024583817) to ensure transparency and enhance accountability throughout the research process. The study design adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [28].

Search strategy

A comprehensive literature search was performed using PubMed, Web of Science, Cochrane Library, and Embase. The search strategy (Supplementary Table 1) combined Medical Subject Headings (MeSH) terms and keywords such as "diclofenac," "topical formulations," "osteoarthritis," "knee," "gel," "solution," "patch," "randomized controlled trial," and "clinical trial," covering publications up to September 2024. Additionally, relevant articles and review references were examined to identify further pertinent literature.

Selection of studies

Studies meeting the PICOS (Population, Intervention, Comparison, Outcomes, and Study Design) criteria (Supplementary Table 2) were included [29]. At this stage, only studies clearly failing to meet the inclusion criteria were excluded. Records deemed potentially relevant or lacking sufficient information in the title or abstract were retained for full-text review. Discrepancies between reviewers regarding study eligibility were resolved through discussion, or by consulting a third reviewer if necessary.

Inclusion criteria were: (1) Study population: patients with knee osteoarthritis; (2) Study groups: topical diclofenac formulation versus placebo; (3) Study design: RCTs; (4) Outcome measures: patient outcomes related to pain, function, or AEs. Exclusion criteria were: (1) Review articles, case series, case reports, letters, or conference abstracts; (2) Use of additional analgesics as adjuvant therapy; (3) Non-placebo control groups; (4) Insufficient or inaccessible data; (5) Duplicate publications. The search was limited to articles published in English.

Data extraction

The data extraction process in this study involved collecting the following information: (1) basic publication details, such as the first author, year of publication, and the country of the corresponding author; (2) demographic characteristics of the subjects, including age, gender, and sample size; (3) the type of topical diclofenac formulation used and the duration of treatment or follow-up; (4) pain relief and functional improvement, assessed by calculating the change from baseline scores at different follow-up time points (short-term: 1–2 weeks, mid-term: 3–6 weeks, long-term: 8–12 weeks). The greater the absolute change in pain and function scores, the better the observed effect. The pain scale most sensitive to change or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was prioritized for evaluating relevant outcomes; if the WOMAC

function score was not reported, the Lequesne Index or other functional measures were used. (5) AEs, including the number of subjects in each group experiencing local skin reactions, GI events, and withdrawals due to AEs, were collected to assess safety. Data extraction was conducted independently by two researchers, and any discrepancies were resolved through discussion or consultation with a third researcher.

Assessment of Article quality

To ensure the validity and reliability of the meta-analysis results, this study used the RoB 2 (Version 2.0) tool to systematically assess the risk of bias in the included randomized controlled trials [30]. Each study was classified as having a "low risk of bias," "some concerns," or "high risk of bias" based on five domains: bias arising from the randomization process, bias due to deviations from intended interventions (including blinding and adherence), bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of the reported results. The quality assessment was conducted independently by two reviewers. Any discrepancies between the reviewers were resolved through discussion, and if a consensus could not be reached, a third reviewer was consulted for arbitration.

Additionally, to evaluate the overall quality of evidence across the outcomes in the meta-analysis, we used the GRADEpro (version 3.6) tool. This tool provides a systematic approach to grading the quality of evidence by considering factors such as risk of bias, consistency, directness, precision, and publication bias. Each outcome's evidence quality was rated as "high," "moderate," "low," or "very low" by two independent researchers, ensuring a thorough and unbiased assessment.

Outcomes and statistical analysis

The primary outcomes of this meta-analysis include pain scores, functional scores, and the incidence of AEs. Pain was assessed using multiple scales, including the 100-mm Visual Analog Scale (VAS), the WOMAC. Functional outcomes were evaluated using the WOMAC function subscale, the Lequesne Index, and AUSCAN function scores. Additionally, the main safety outcomes included the incidence of local skin adverse reactions, GI adverse events, and the number of participants who withdrew due to AEs. Secondary outcomes included the relief of stiffness, pain reduction during walking, Patient Global Assessment (PGA) scores, and the incidence of other AEs not classified as primary outcomes. For studies with missing data, we initially contacted the corresponding authors to obtain any available information. If this was unsuccessful, missing values were calculated from other available data using formulas outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

A random-effects model was used for the meta-analysis to account for potential heterogeneity between studies. For continuous outcomes (e.g., pain and functional scores), the standardized mean difference (SMD) and its 95% confidence interval (CI) were calculated. For dichotomous outcomes (e.g., AEs and withdrawal rates), odds ratios (OR) and their 95% CI were computed. Heterogeneity across studies was assessed using the I^2 statistic, where I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively [31]. In cases of significant heterogeneity ($I^2 > 50\%$), subgroup analyses and sensitivity analyses were conducted to explore potential sources [32]. All statistical analyses were performed using software such as Review Manager version 5.2 (RevMan 5.2, The Cochrane Collaboration, Oxford, UK) and STATA version 12.0 (StataCorp LP, College Station, TX).

Results

Characteristics of the included studies

The process of study selection is shown in Fig. 1. In the initial search, a total of 1,188 studies were identified from multiple databases, including PubMed, Embase, and the Cochrane Library. After removing duplicate studies and excluding 250 irrelevant articles based on title and abstract screening, 77 studies remained for further evaluation. Upon reviewing the titles and abstracts, studies that did not meet the predefined inclusion criteria were excluded, such as those unrelated to KOA, involving systemic administration of diclofenac, or not reporting relevant outcomes. Ultimately, 12 studies were deemed eligible for inclusion in this meta-analysis and proceeded to full-text review (Table 1) [15, 17–27].

Risk of bias

Based on the risk of bias assessment, the majority of the included RCTs demonstrated a low risk of bias (Supplementary Fig. 1). Specifically, 9 out of 12 studies [15, 17, 19–23, 26, 27] were rated as having a low risk of bias, indicating a high methodological quality. Two studies [18, 24] raised some concerns regarding deviations from intended interventions. One study [25] showed concerns related to both the randomization process and deviations from intended interventions. Overall, most studies indicated a low risk of selective reporting bias, ensuring the reliability of the results.

Outcomes of meta-analysis

Pain relief at 1–2 weeks

A total of 5 studies assessed pain relief at 1–2 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (SMD: -0.46; 95% CI: -0.72 to -0.20; I^2= 70%; Z = 3.52; P = 0.0004) (Fig. 2). Subgroup analysis revealed that both Diclofenac gel (3 studies, SMD: -0.34; 95% CI:

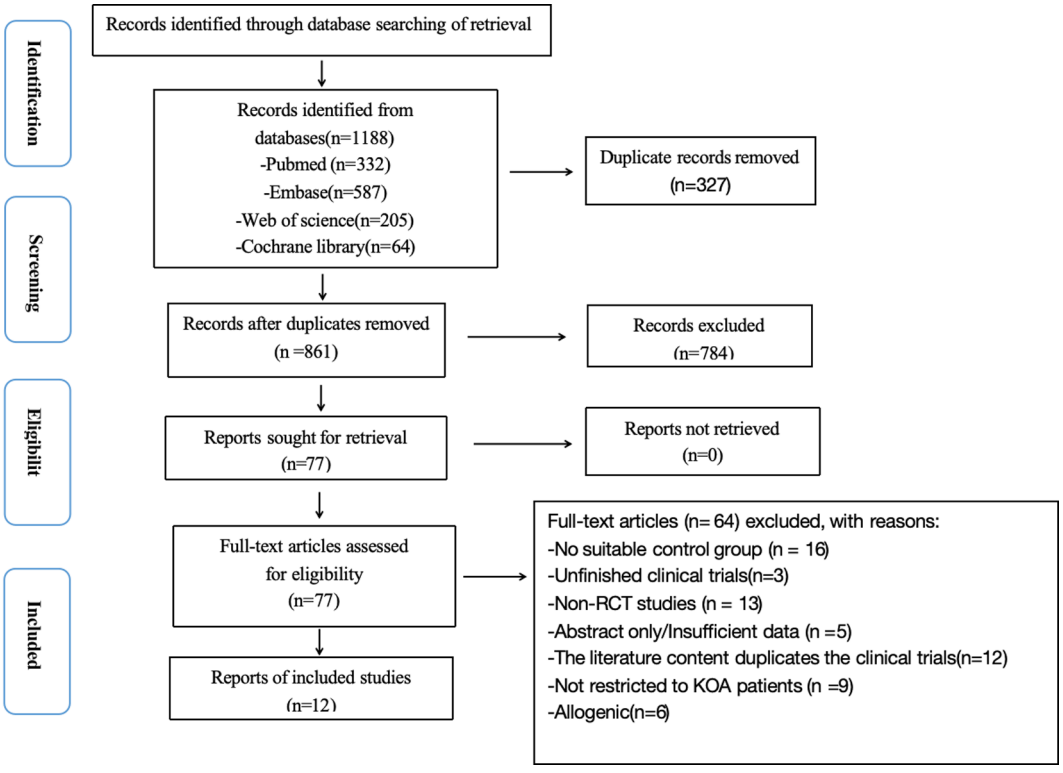

Fig. 1 Selection process for systematic review

-0.64 to -0.04; I^2 = 69%; Z = 2.20; *P* = 0.03) and Diclofenac patch (2 studies, SMD: -0.64; 95% CI: -0.90 to -0.39; I^2 = 0%; Z = 4.90; *P* < 0.00001) were associated with significantly improved pain relief compared to placebo, with the Diclofenac patch showing a slightly larger effect size and no observed heterogeneity (I^2= 0%).

Pain relief at 3–6 weeks

A total of 7 studies assessed pain relief at 3–6 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (SMD: -1.25; 95% CI: -1.79 to -0.71; I^2= 18%; Z = 4.53; *P* < 0.00001) (Fig. 3). Subgroup analysis revealed that both Diclofenac gel (4 studies, SMD: -1.43; 95% CI: -2.34 to -0.51; I^2= 55%; Z = 3.06; *P* = 0.002) and Diclofenac solution (3 studies, SMD: -1.15; 95% CI: -1.82 to -0.48; I^2= 0%; Z = 3.37; *P* = 0.0007) were associated with significantly improved pain relief compared to placebo. The Diclofenac gel showed moderate heterogeneity (I^2= 55%), whereas no heterogeneity was observed for Diclofenac solution (I^2 = 0%).

Pain relief at 8-12Weeks

A total of 4 studies assessed pain relief at 8–12 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (Mean Difference: -1.51; 95% CI: -2.05 to -0.96; I^2 = 0%; Z = 5.44; *P* < 0.00001) (Fig. 4). Subgroup analysis revealed that both Diclofenac gel (2 studies, Mean Difference: -1.31; 95% CI: -2.06 to -0.56; I^2 = 0%; Z = 3.40; *P* = 0.0007) and Diclofenac solution (2 studies, Mean Difference: -1.72; 95% CI: -2.50 to -0.94; I^2 = 0%; Z = 4.31; *P* < 0.0001) were associated with significantly improved pain relief compared to placebo. Both subgroups exhibited no observed heterogeneity (I^2= 0%), suggesting consistent effects across studies for both formulations.

Function improvement at 1–2 weeks

A total of 5 studies assessed function improvement at 1–2 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (SMD: -0.40; 95% CI: -0.68 to -0.12; I^2= 75%; Z = 2.83; *P* = 0.005) (Fig. 5). Subgroup analysis revealed that Diclofenac gel (3 studies, SMD: -0.48; 95% CI: -0.91 to -0.05; I^2 = 84%; Z = 2.17; *P* = 0.03) was associated with significantly improved function compared to placebo, while Diclofenac patch (2 studies, SMD: -0.34; 95% CI: -0.79 to 0.12; I^2= 68%; Z = 1.45; *P* = 0.15) did not show a statistically significant difference. The Diclofenac gel subgroup showed substantial heterogeneity (I^2= 84%), while the Diclofenac patch subgroup had moderate heterogeneity (I^2= 68%).

Table 1 Characteristics of studies on osteoarthritis treatment using topical diclofenac

Characteristics	Niethard (2005)	Barthel (2009)	Baraf (2010)	Shoara (2015)	Bihlet (2020)	Bookman (2004)	Roth (2004)	Baer (2005)	Simon (2009)	Wadsworth (2016)	Dreiser (1993)	Brühlmann (2003)
Country	Germany	Australia	USA	Iran	Denmark	Canada	USA	Canada	Canada	USA	France	Switzerland
Journal	J Rheumatol	Semin Arthritis Rheu	Phys Sportsmed	Complement Ther Clin	Semin Arthritis Rheu	CMAJ	Arch Intern Med	BMC Musculoskelet Disord	Pain	Curr Med Res Opin	Drugs Exp Clin Res	Clin Exp Rheumatol
Sample sizes, (n)												
Study	117	254	208	28	297	84	164	107	154	130	78	51
Control	120	238	212	28	147	80	162	109	161	129	77	52
Age, (years), mean ± SD												
Study	66 ± 9	59.7 ± 9.2	71.8 ± 5.4	52.7 ± 6.1	65 ± 10.7	62.5 ± 11.7	63.4 ± 10.5	65.0 ± 11.0	61.7 ± 9.8	60.2 ± 9.2	66.7 ± 9.5	64.0 ± 10.7
Control	65 ± 9.1	59.2 ± 6.1	72.1 ± 5.3	52.0 ± 6.3		60.8 ± 11.4	64.9 ± 10.6	64.6 ± 10.9	62.1 ± 9.3	61.9 ± 9.1	64.5 ± 10	64.8 ± 10.6
Gender, (Female %)	62	67.3	60.6	75.0	66.9	62	68.9	52.3	67.5	64.6	74.4	53
	65	65.5	66.5	85.7		68	66.7	60.6	55.9	69.8	80.5	64
Target joint	Knee	Knee	Knee	Knee	Knee	Knee	Knee	Knee	Knee	Knee	Knee	Knee
K-L grade	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III	I, II, III
Diclofenac Form	Diclofenac gel	Diclofenac gel	Diclofenac gel	Diclofenac gel	Diclofenac gel	Diclofenac solution	Diclofenac solution	Diclofenac solution	Diclofenac solution	Diclofenac solution	Diclofenac patch	Diclofenac patch
Control	Placebo	Placebo (Vehicle)	Placebo (Vehicle)	Placebo	Placebo (Vehicle)	Placebo (Vehicle)	Placebo (Vehicle)	Placebo (Vehicle)	Placebo (Vehicle)	Placebo (Vehicle)	Placebo	Placebo
Dosage/Concentration	1.16% (4 g), 4 times daily, 3 weeks	1% (4 g), 4 times daily, 12 weeks	1% (4 g), 4 times daily, 12 weeks	X% (X g), 3 times daily, 3 weeks	1.5% (40 drops), 4 times daily, 4 weeks	1.5% (40 drops), 4 times daily, 12 weeks	1.5% (40 drops), 4 times daily, 6 weeks	1.5% (40 drops), 4 times daily, 12 weeks	2% (2 ml), 2 times daily, 4 weeks	(40 drops) 4 times daily, 6 weeks	Diclofenac patch, 2 times daily, 2 weeks	Diclofenac patch, 2 times daily, 2 weeks
Mean FU periods (weeks, range)	3	12	12	3	4	12	6	12	4	6	2	2

FU, follow-up; K-L grade, Kellgren-Lawrence grade; X% (X g), not reported

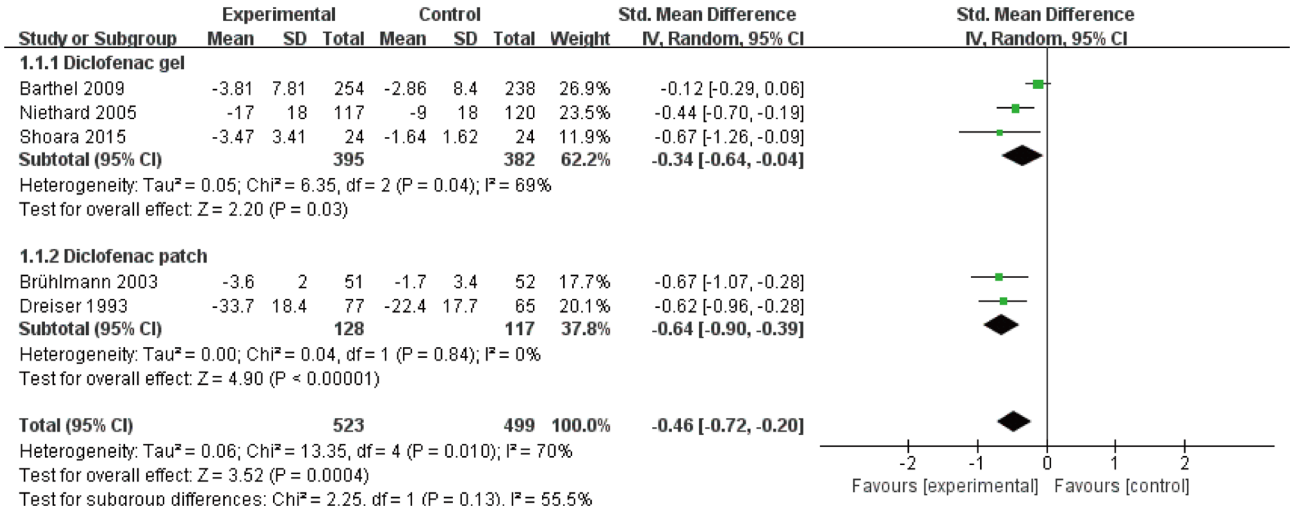

Fig. 2 Meta-analysis of pain relief at 1–2 weeks for the diclofenac gel and diclofenac patch subgroups

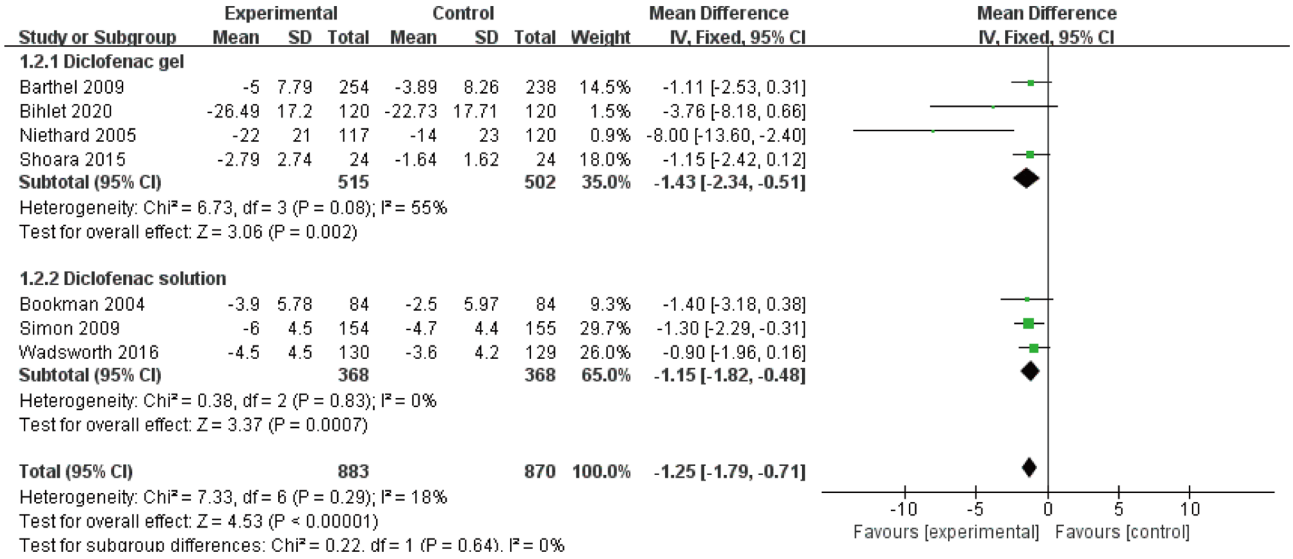

Fig. 3 Meta-analysis of pain relief at 3–6 weeks for the diclofenac gel and diclofenac solution subgroups

Function improvement at 3–6 weeks

A total of 7 studies assessed function improvement at 3–6 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (SMD: -0.23; 95% CI: -0.33 to -0.14; I^2= 0%; Z = 4.85; $P < 0.00001$) (Fig. 6). Subgroup analysis revealed that Diclofenac gel (4 studies, SMD: -0.28; 95% CI: -0.45 to -0.10; I^2 = 42%; Z = 3.06; $P < 0.002$) and Diclofenac solution (3 studies, SMD: -0.22; 95% CI: -0.36 to -0.07; I^2= 0%; Z = 2.93; $P = 0.003$) were both associated with significantly improved function compared to placebo. Both subgroups exhibited no significant heterogeneity, with Diclofenac gel showing low heterogeneity (I^2= 42%) and Diclofenac solution showing no heterogeneity (I^2= 0%).

Function improvement at 8–12 weeks

A total of 4 studies assessed function improvement at 8–12 weeks, demonstrating a significantly greater mean improvement in the Diclofenac treatment groups compared to the placebo groups (SMD: -0.29; 95% CI: -0.41 to -0.17; I^2= 23%; Z = 4.73; $P < 0.00001$) (Fig. 7). Subgroup analysis revealed that Diclofenac gel (2 studies, SMD: -0.22; 95% CI: -0.37 to -0.07; I^2= 24%; Z = 2.91; $P = 0.004$) and Diclofenac solution (2 studies, SMD: -0.39; 95% CI: -0.56 to -0.22; I^2= 0%; Z = 4.48; $P < 0.00001$) were both associated with significantly improved function compared to placebo. Both subgroups exhibited no significant heterogeneity, with Diclofenac gel showing low heterogeneity (I^2= 24%) and Diclofenac solution showing no heterogeneity (I^2= 0%).

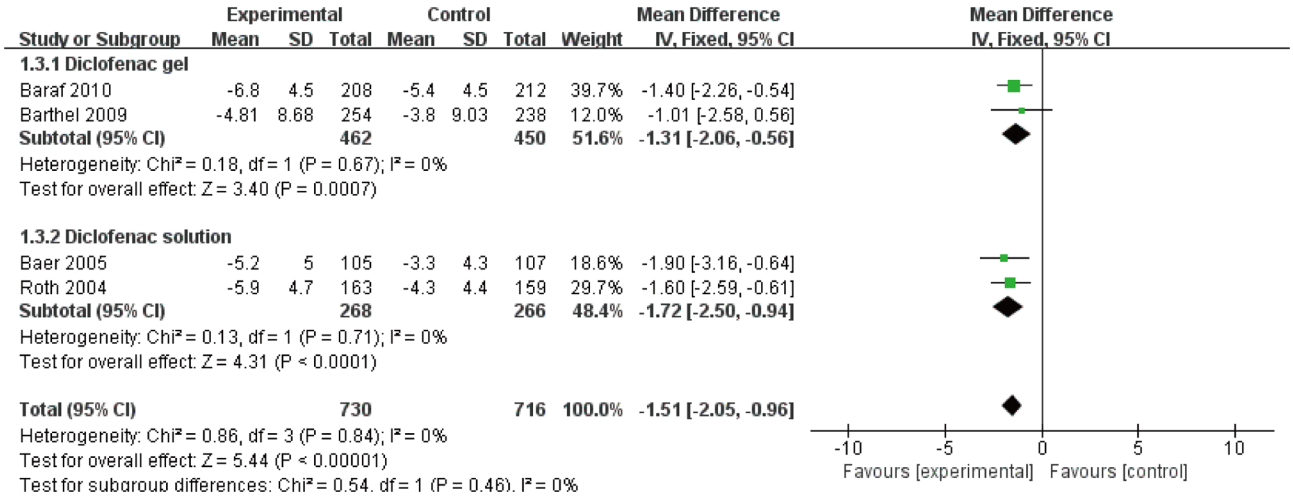

Fig. 4 Meta-analysis of pain relief at 8–12 Weeks for the diclofenac gel and diclofenac solution subgroups

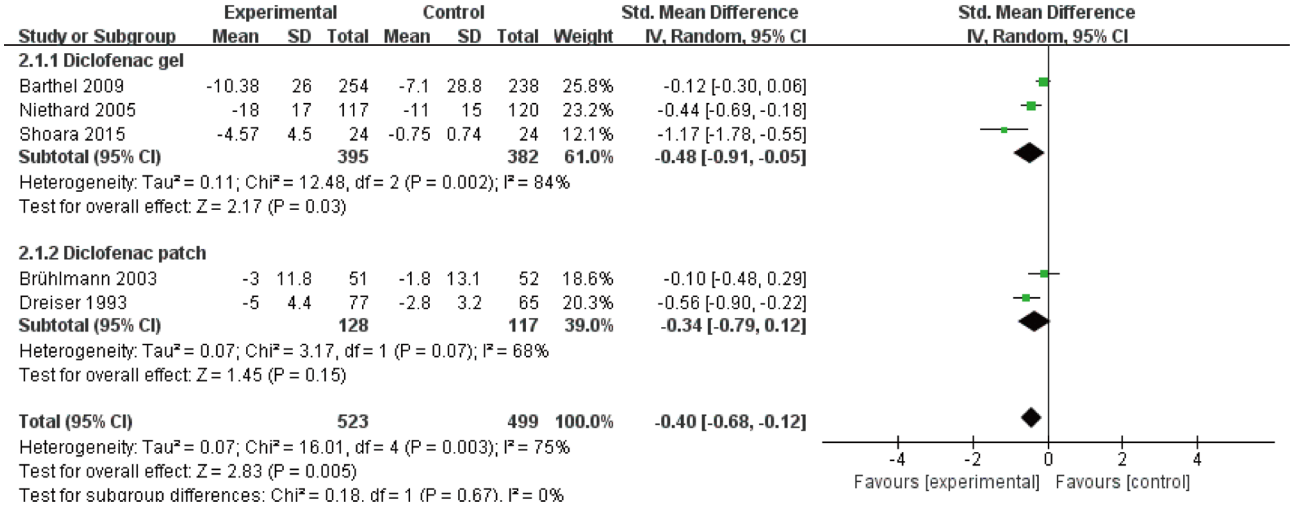

Fig. 5 Meta-analysis of function improvement at 1–2 Weeks for the diclofenac gel and diclofenac patch subgroups

Other pain and functional outcomes

Due to the limitations of the outcome assessment methods, a meta-analysis of other indicators for the patch could not be performed. Therefore, this meta-analysis only evaluated the efficacy of diclofenac gel and diclofenac solution on various pain and functional outcomes at multiple time points (Supplementary Figs. 2–7) (1–2 weeks, 3–6 weeks, and 8–12 weeks). Both dosage forms consistently demonstrated significant treatment benefits across several key outcomes with overall low heterogeneity, indicating the reliability and consistency of their effects. At 1–2 weeks, stiffness relief was significantly improved with both Diclofenac gel and solution compared to placebo, showing a pooled effect size of SMD: -0.21 (95% CI: -0.34 to -0.09) and no heterogeneity (I^2 = 0%). Similarly, at 3–6 weeks, the pooled effect size for stiffness relief was SMD: -0.25 (95% CI: -0.42 to -0.07), with moderate heterogeneity (I^2 = 43%), further supporting the robustness of the findings. Pain relief during walking was also notably improved at both 3–6 weeks and 8–12 weeks, with pooled effect sizes of SMD: -0.28 and SMD: -0.28, respectively, demonstrating sustained efficacy over time without heterogeneity. Patient global assessment scores were significantly better in the Diclofenac groups compared to placebo at both 3–6 weeks (SMD: -0.22; 95% CI: -0.32 to -0.12) and 8–12 weeks (SMD: -0.27; 95% CI: -0.41 to -0.13), with no significant heterogeneity (I^2 = 0%).

Adverse reactions

In the meta-analysis of skin AEs, the diclofenac gel subgroup showed no significant difference in risk compared to the placebo group, with an odds ratio (OR) of 2.34 (95% CI: 0.53–10.36, $p = 0.26$), and low heterogeneity among studies (I^2 = 65%). The solution and patch subgroups did not show statistically significant increases in

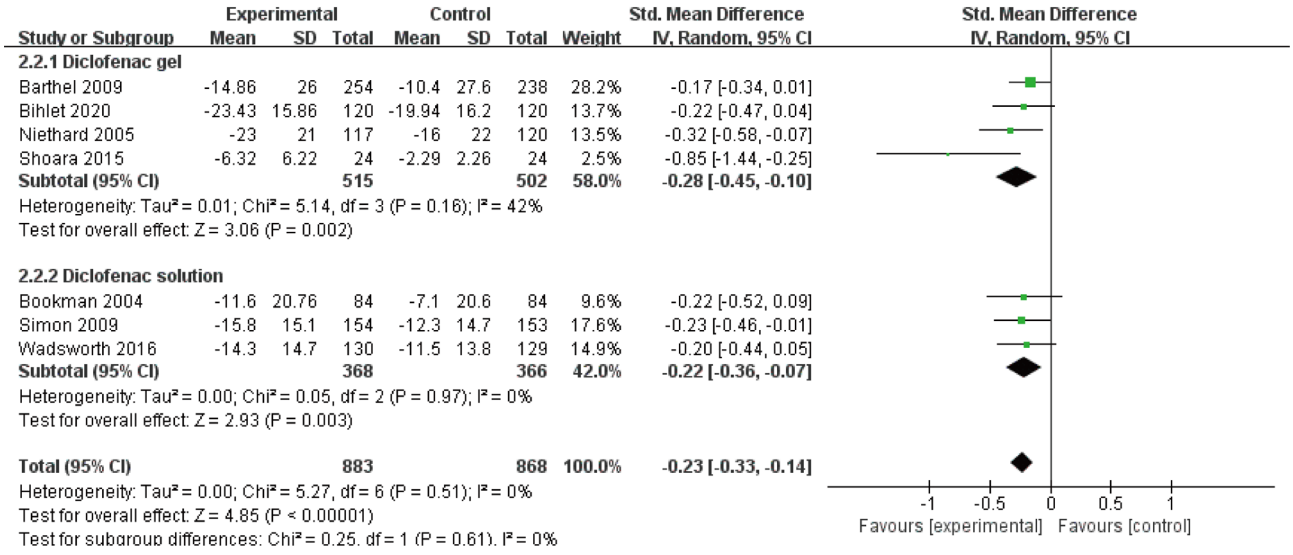

Fig. 6 Meta-analysis of Function improvement at 3–6 Weeks for the Diclofenac gel and Diclofenac solution subgroups

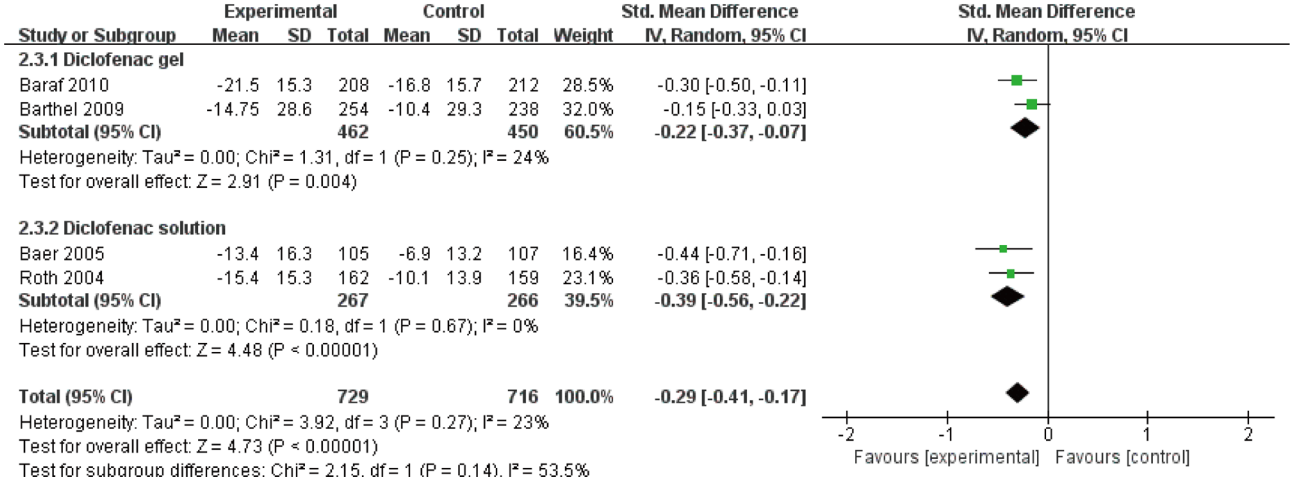

Fig. 7 Meta-analysis of function improvement at 8–12 weeks for the diclofenac gel and diclofenac solution subgroups

skin AEs, with ORs of 1.47 (95% CI: 0.71–3.07, $p = 0.30$) and 1.02 (95% CI: 0.24–4.41, $p = 0.98$), respectively (Supplementary Fig. 8). For GI adverse effects, none of the subgroups (gel, solution, or patch) showed a significant increase, with a pooled OR of 1.00 (95% CI: 0.66–1.52, $p = 0.99$), and no heterogeneity (I^2 = 0%) (Supplementary Fig. 9). Regarding withdrawal due to AEs, the OR for the gel subgroup was 1.91 (95% CI: 0.92–3.94, $p = 0.08$), 1.41 (95% CI: 0.85–2.35, $p = 0.19$) for the solution subgroup, and 0.43 (95% CI: 0.06–2.97, $p = 0.39$) for the patch subgroup. The pooled analysis did not indicate a significant difference (OR: 1.49, 95% CI: 1.02–2.17, $p = 0.04$) (Supplementary Fig. 10). Table 2 provides other AEs reported in these studies, all of which were considered unrelated to the medication.

In summary, the meta-analysis results indicated no significant differences in the risk of skin AEs across the diclofenac gel, solution, and patch subgroups compared to placebo. No significant increases were found in GI adverse effects or withdrawal rates across all subgroups. These findings suggest that the external formulations of diclofenac are generally well-tolerated, with a relatively low risk of systemic adverse effects.

Sensitivity analysis

This sensitivity analysis plot examines the impact of omitting each individual study on the overall meta-analysis estimates (Supplementary Fig. 11). The plot shows that the exclusion of any single study does not significantly alter the overall effect estimate, as the CIs remain within a similar range. The estimates after omitting each study fall between −0.33 and −0.14, suggesting that the results of the meta-analysis are robust and not unduly

Table 2 Adverse (Except for skin and Gastrointestinal adverse reactions) and serious adverse events in the included studies

Lead author (Year)	Diclofenac dosage form	Adverse events / cases	Serious adverse events(All are considered unrelated to the drug application) / cases
Niethard (2005)	gel	None	None
Barthel (2009) [27]	gel	Cardiovascular adverse: 4; Headache:34; Arthralgia:35; Back pain:23; Infection(Sinusitis/Cough):10; Nasopharyngitis:9; Pain in extremity:10; pain:11; Upper respiratory tract infection:9.	16
Baraf (2010) [17]	gel	Headache:30; Arthralgia:13; Back pain:11; Nasopharyngitis:4; Pain in extremity:8; Neck pain:7; pain:7; Upper respiratory tract infection:6.	17
Shoara (2015) [18]	gel	None	None
Bihlet (2020) [19]	gel	Headache:2; Infection(Sinusitis/Cough):18; Nasopharyngitis:6.	None
Simon (2009) [23]	solution	Headache:27; Arthralgia:14; Back pain:15; pain:7; Upper respiratory tract infection:5.	0

influenced by any single study. This confirms the stability and reliability of the pooled effect size in the analysis.

Subgroup analysis, meta regression results

Supplementary Table 3 presents the summary results of the subgroup analyses. Supplementary Table 4 summarizes the meta-regression analysis, revealing no significant sources of heterogeneity.

Quality of the evidence and recommendation strengths

The quality of the evidence was either moderate or high, with no very low-quality evidence found. Therefore, we conclude that the overall quality of the evidence is moderate to high, indicating that the actual effects are likely to be close to the estimated effects. The results show that diclofenac topical formulations provide reliable short-term effects in pain relief and function improvement, particularly at 1–2 weeks and 8–12 weeks. However, for AEs such as skin and GI issues, the evidence is moderate, suggesting the need for moderate attention to safety risks (Supplementary Tables 5 and 6).

Discussion

This meta-analysis comprehensively reveals the efficacy and safety of different topical dosage forms of diclofenac sodium (gel, solution, and patch) in the treatment of KOA. Overall, the results demonstrate that all three dosage forms significantly improve pain relief and functional improvement in patients with KOA, with notable efficacy observed at different time points (short-term: 1–2 weeks, mid-term: 3–6 weeks, long-term: 8–12 weeks) when compared to the placebo group. In the short-term (1–2 weeks), the diclofenac patch showed a slightly greater effect size. However, it is important to note that the patch was excluded from the mid- and long-term efficacy analyses due to the 2-week follow-up period in the available patch studies. In terms of functional improvement, both diclofenac gel and solution exhibited significant benefits during mid- and long-term follow-ups. This analysis also highlights the safety profile of these topical formulations. None of the three formulations showed a significant increase in skin AEs, GI adverse events or treatment discontinuation due to AEs. This suggests that topical diclofenac is a relatively safer alternative for patients requiring long-term pain management, though skin reactions should be closely monitored. Our findings align with previous studies on the use of topical NSAIDs for OA, which have demonstrated significant pain relief and functional improvement with reduced systemic side effects [33–35]. However, this meta-analysis provides a more comprehensive understanding by directly comparing different formulations—gel, solution, and patch.

The slightly greater short-term efficacy of the diclofenac patch is consistent with previous research suggesting that the patch may offer more sustained drug delivery due to occlusive bandaging and slower drug release, which may explain its superiority in short-term efficacy.[36] An innovative aspect of this analysis is the finding that while both diclofenac gel and solution are effective in the mid- and long-term, the solution formulation shows more consistent benefits due to better absorption and less variation in use. These formulation differences offer clearer clinical guidance, helping clinicians make better choices in different clinical contexts.

The results of this meta-analysis are of great significance for optimizing clinical treatment of KOA. Given the effectiveness of all three formulations, clinicians can choose the most appropriate treatment based on the individual characteristics of the patient, especially given that no significant differences in skin reactions were observed across the diclofenac gel, solution, or patch formulations compared to placebo. This suggests that all

three formulations are similarly tolerable, and patients can select the most suitable option based on personal preference or convenience. Moreover, the findings support the use of topical diclofenac as a viable option for long-term pain management in KOA, particularly for patients at risk of GI issues with oral NSAIDs. Additionally, the lower incidence of GI side effects with all topical formulations suggests that these therapies may be safer options for elderly patients or those with a history of GI disorders.

Despite the significant value of this meta-analysis, some limitations must be acknowledged. The included studies varied in treatment duration, patient characteristics, and evaluation methods, which may contribute to heterogeneity in the results. Additionally, although the risk of bias assessment in this study indicates that most of the included studies had a low risk of bias, we acknowledge that some of these studies were sponsored by manufacturers, which may introduce potential bias in the interpretation of the results, particularly when these studies are used for regulatory purposes. While no direct evidence of selective reporting bias was identified, the potential bias associated with manufacturer sponsorship warrants attention. This should be considered an important focus for future large-scale, independent studies to further validate the efficacy and safety of topical diclofenac in the treatment of KOA.

Conclusions

In conclusion, this meta-analysis indicates that the different topical dosage forms of diclofenac sodium—gel, solution, and patch—are effective and safe for relieving KOA symptoms, particularly in terms of pain relief and functional improvement. All three formulations demonstrate efficacy. The patch is more effective in the short term (up to 2 weeks), while the solution provides more consistent benefits over the long term. Compared to placebo, the three diclofenac formulations are associated with a lower risk of local skin adverse events and a similarly low risk of systemic side effects. These findings offer clear clinical guidance for selecting the appropriate diclofenac formulation for KOA patients, aiding in the development of personalized treatment strategies that balance efficacy with the risk of AEs.

Abbreviations

OA	Osteoarthritis
KOA	Knee Osteoarthritis
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
COX	Cyclooxygenase
RCTs	Randomized Controlled Trials
SMD	Standardized Mean Difference
CI	Confidence Interval
AEs	Adverse Events
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
AUSCAN	Australian/Canadian Osteoarthritis Hand Index
PGA	Patient Global Assessment
OR	Odds Ratio
GI	Gastrointestinal
PICOS	Population Intervention Comparison Outcomes and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions

Conceptualization: P-L.Search: BK-C. Data Extraction and quality assessment: P-L and BK-C. Statistical analysis: K-F.Writing: P-L, BK-C.Supervision and modification: ZR-C. ZR-C and BK-C contributed equally to the study.All authors read and approved the final version of this paper.

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Data availability

All data and materials are contained within the manuscript and its additional files.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare no competing interests.

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