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ORIGINAL ARTICLE

Rectal Diclofenac Versus Indomethacin in Preventing Post-ERCP Pancreatitis: A Systematic Review and Meta-Analysis

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Abstract

Introduction Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) affects up to 9% of average-risk and 40% of high-risk patients. Rectal NSAIDs are guideline-recommended for PEP prophylaxis, yet direct evidence comparing different NSAIDs remains scarce. This study systematically evaluates head-to-head evidence to compare the efficacy of rectal diclofenac versus indomethacin in the prevention of PEP.

Methodology This systematic review and meta-analysis adhered to the PRISMA guidelines and was prospectively registered in PROSPERO (CRD420251107055). Eligible studies directly compared rectal diclofenac versus indomethacin for PEP prevention in adults undergoing ERCP. A comprehensive search of five databases was performed through July 2025. Pooled risk ratios with 95% CIs were calculated using fixed- or random-effects models based on heterogeneity, and certainty of evidence was assessed using the GRADE approach.

Results Four studies (three RCTs, one observational; n = 2,917) compared rectal diclofenac (n = 1,275) and indomethacin (n = 1,642) for PEP prevention. Baseline characteristics were comparable, except for less frequent balloon dilatation with diclofenac (RR 0.78, 95% CI 0.68–0.89; $p < 0.001$). No significant differences were found for overall PEP (RR 1.17, 95% CI 0.92–1.49; $I^2 = 0\%$), mild PEP (RR 1.24, 95% CI 0.94–1.63; $I^2 = 0\%$), moderate PEP (RR 0.60, 95% CI 0.21–1.73; $I^2 = 0\%$), severe PEP (RR 1.09, 95% CI 0.32–3.77; $I^2 = 1\%$), or moderate-to-severe PEP (RR 0.97, 95% CI 0.46–2.05; $I^2 = 0\%$). Secondary outcomes, including mortality and complications, were also similar, with low heterogeneity, indicating equivalent efficacy and safety.

Conclusion Diclofenac and indomethacin demonstrate equivalent efficacy and safety, allowing cost and availability to inform the choice of PEP prophylaxis.

Keywords Cholangiopancreatography · Endoscopic retrograde · Pancreatitis · Diclofenac · Indomethacin

Abbreviations

ERCP	Endoscopic retrograde cholangiopancreatography
PEP	Post-Endoscopic retrograde cholangiopancreatography pancreatitis
NSAIDs	Non-steroidal anti-inflammatory drugs
CoE	Certainty of evidence

Introduction

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) remains the most common complication of ERCP, converting a minimally invasive therapeutic procedure into a potentially life-threatening condition. PEP affects up to 9% of average-risk and 40% of high-risk patients, with severe cases leading to necrosis, organ failure, or death [1, 2]. A history of pancreatitis, sphincterotomy or cannulation, and trainee involvement are recognized risk factors for PEP [3]. Prophylactic pancreatic duct stenting has demonstrated efficacy in high-risk patients, but its technical demands, cost, and risk of ductal injury limit its widespread use [4].

Extended author information available on the last page of the article

Rectal non-steroidal anti-inflammatory drugs (NSAIDs), have become the cornerstone of pharmacologic PEP prevention due to their anti-inflammatory action and favorable safety profile. Their use, especially in high-risk patients, is supported by several meta-analyses and guidelines [5–7]. However, previous analyses have often grouped NSAIDs as a class, rather than offering direct head-to-head comparisons, thereby limiting drug-specific insights [8, 9]. The first RCT comparing rectal indomethacin and diclofenac for PEP was limited to a single center [10]. More recently, the DIPPP trial (2025) was conducted across nine endoscopic centers in China, marking a considerable, multicenter effort to compare rectal diclofenac and indomethacin for the prevention of PEP [11]. The significance of the rectal route in achieving therapeutic tissue levels and facilitating rapid drug delivery was emphasized in a 2025 analysis by Swaminathan et al. [12].

Unlike earlier meta-analyses that pooled NSAIDs as a class, our analysis aims to reduce heterogeneity arising from pharmacokinetic and pharmacodynamic differences, such as diclofenac's faster absorption compared to indomethacin's longer half-life [11, 13]. Additionally, if established as non-inferior to indomethacin, diclofenac's comparatively lower production and acquisition costs may inform clinical and policy decisions [12].

Methodology

We conducted and reported this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The protocol for this study was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO), under CRD420251107055.

Eligibility Criteria

Studies were eligible for inclusion based on the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework. We included studies involving adult patients undergoing ERCP (Population), in which rectal diclofenac was administered as prophylaxis (Intervention) and compared to rectal indomethacin (Comparator). The primary outcome was the incidence of PEP. Eligible study designs included randomized controlled trials (RCTs) and observational studies reporting original data. Studies were excluded if they did not provide a direct comparison between rectal diclofenac and indomethacin. Narrative reviews, meta-analyses, editorials, case reports, commentaries, animal study designs, and conference abstracts were excluded from the analysis.

Search Strategy and Data Extraction

Four independent reviewers systematically searched five electronic databases—PubMed, Embase, ScienceDirect, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov—from inception to July [2025], without applying language restrictions. The search strategy combined Medical Subject Headings (MeSH) and relevant keywords, including "Cholangiopancreatography, Endoscopic Retrograde," "Diclofenac," "Indomethacin," and "Pancreatitis". In addition, we conducted a supplementary citation search using literature maps (app.litmaps.com, Litmaps Ltd, Wellington, Newzealand). The complete electronic search strategy for each database is detailed in Supplementary Table S1. All retrieved records were imported into Covidence for screening and deduplication. Two reviewers independently screened titles and abstracts against predefined inclusion criteria, followed by full-text review of shortlisted studies. Any discrepancies were resolved through discussion or adjudication by a third reviewer (MA).

Data Extraction and Outcomes

A standardized data extraction template was developed to collect information on (1) study characteristics, (2) baseline population and intervention details, and (3) study outcomes. Data extraction was performed independently by two reviewers for each included study, with discrepancies resolved through discussion with a third reviewer (MA). The primary outcomes of this study were the incidence and severity of PEP in patients receiving rectal diclofenac versus indomethacin. Severity was categorized as mild, moderate, or severe according to standard clinical definitions. Secondary outcomes included all-cause mortality, gastrointestinal bleeding, biliary tract infection, perforation, overall complication rates, and other procedure-related adverse events.

Risk of Bias and GRADE Assessment

Risk of bias was assessed using the Cochrane Risk of Bias tool (RoB 2.0) for randomized controlled trials, which evaluates five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. For non-randomized studies, the Risk Of Bias In Non-Randomized Studies–of Interventions (ROBINS-I) tool was applied, covering seven domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result. Certainty of evidence(CoE) for each outcome was

evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. GRADE considers factors such as study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, and other relevant criteria to categorize the certainty of evidence as high, moderate, low, or very low.

Statistical Analysis

Meta-analyses were conducted by pooling outcomes using both fixed-effect and random-effects models, depending on the degree of heterogeneity. Statistical heterogeneity across studies was assessed using the I^2 statistic and Cochran's Q test. A fixed-effects model was applied when statistical heterogeneity was low ($I^2 \leq 50\%$), whereas a random-effects model (DerSimonian and Laird method) was used when heterogeneity was moderate to high ($I^2 > 50\%$). Dichotomous outcomes were synthesized as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Sensitivity analyses were performed using a leave-one-out approach. Publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's regression test. A p-value < 0.05 was considered statistically significant. All analyses were performed using Review Manager (RevMan) version 7.2.0 by reviewer ZA.

Results

Study Screening and Selection Process

During the screening process, 445 records were identified through five search databases: Embase (n = 211), Cochrane Library (n = 67), PubMed (n = 54), ScienceDirect (n = 16), and ClinicalTrials.gov (n = 3). Additionally, 78 records were identified through citation searching. After removing 81 duplicates, 364 records were screened. After title and abstract screening, 345 records were excluded, and 19 full-text articles were assessed for eligibility. Of these, 15 studies were excluded due to mismatched PICO elements (n = 12) and being conference abstracts (n = 3). Ultimately, four studies were included in the final qualitative and quantitative synthesis (Fig. 1). Characteristics of abstracts that met PICO criteria but were excluded from the primary analysis due to lack of peer review are summarized in Supplementary Table S2. The corresponding forest plot, combining their data with our primary synthesis for overall PEP, is presented in Supplementary Figure S1. Due to the limited number of included studies (n = 4), formal assessments of small-study effects, including funnel plot visualization and Egger's regression test, were not performed, in line with recommended methodological standards.

Due to the limited number of included studies (n = 4), formal assessments of small-study effects, including funnel plot visualization and Egger's regression test, were not performed, in line with recommended methodological standards.

Study Characteristics

A total of four studies (three Randomized Controlled Trials [RCTs] and one retrospective cohort study), published online between 2016 and 2025, met the inclusion criteria and were included in this meta-analysis, encompassing 2,917 patients (Diclofenac, n = 1,275; indomethacin, n = 1,642). The DIPP trial was designed as a superiority trial comparing diclofenac with indomethacin [11]. The control was consistent across all included studies, except for Wu X et al. [15] which also incorporated a combined therapy group that received both indomethacin and diclofenac. The comprehensive details of the baseline characteristics of all included studies are mentioned in Table 1.

Quality and GRADE Assessment

All three randomized controlled trials, Wu X et al. (2025) [15], Kang X et al. (2025) [11], and Alizadeh AH et al. (2016) [10], were assessed as having a low risk of bias based on the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. The non-comparative observational study by Janssens LP et al. (2024) [12] was evaluated using the ROBINS-I tool and judged to have a moderate risk of bias (Supplementary Figure S2).

The CoE for all primary outcomes (overall PEP, mild PEP, moderate PEP, severe PEP, and moderate-to-severe PEP) was assessed using the GRADE criteria within the available studies (Table 2). The analysis revealed a moderate CoE for overall and mild PEP, with downgrading attributed to CI boundaries crossing the predefined threshold of effect size. The CoE for moderate, severe, and moderate-to-severe PEP was deemed low, primarily due to very serious imprecision resulting from low event rates and wide CIs that encompassed both potential benefits and harms. For secondary outcomes, the CoE for bleeding, biliary tract infection, overall complications, and other complications was moderate, with downgrading due to imprecision. Mortality and perforation demonstrated low CoE, predominantly due to very serious imprecision arising from small sample sizes and wide CIs.

Baseline Procedural Characteristics

The baseline characteristics analysis indicated that the diclofenac and indomethacin groups were largely similar on all assessed parameters, except for balloon dilatation of the native papilla. Among patient-related risk factors, no statistically significant imbalance was found for history of

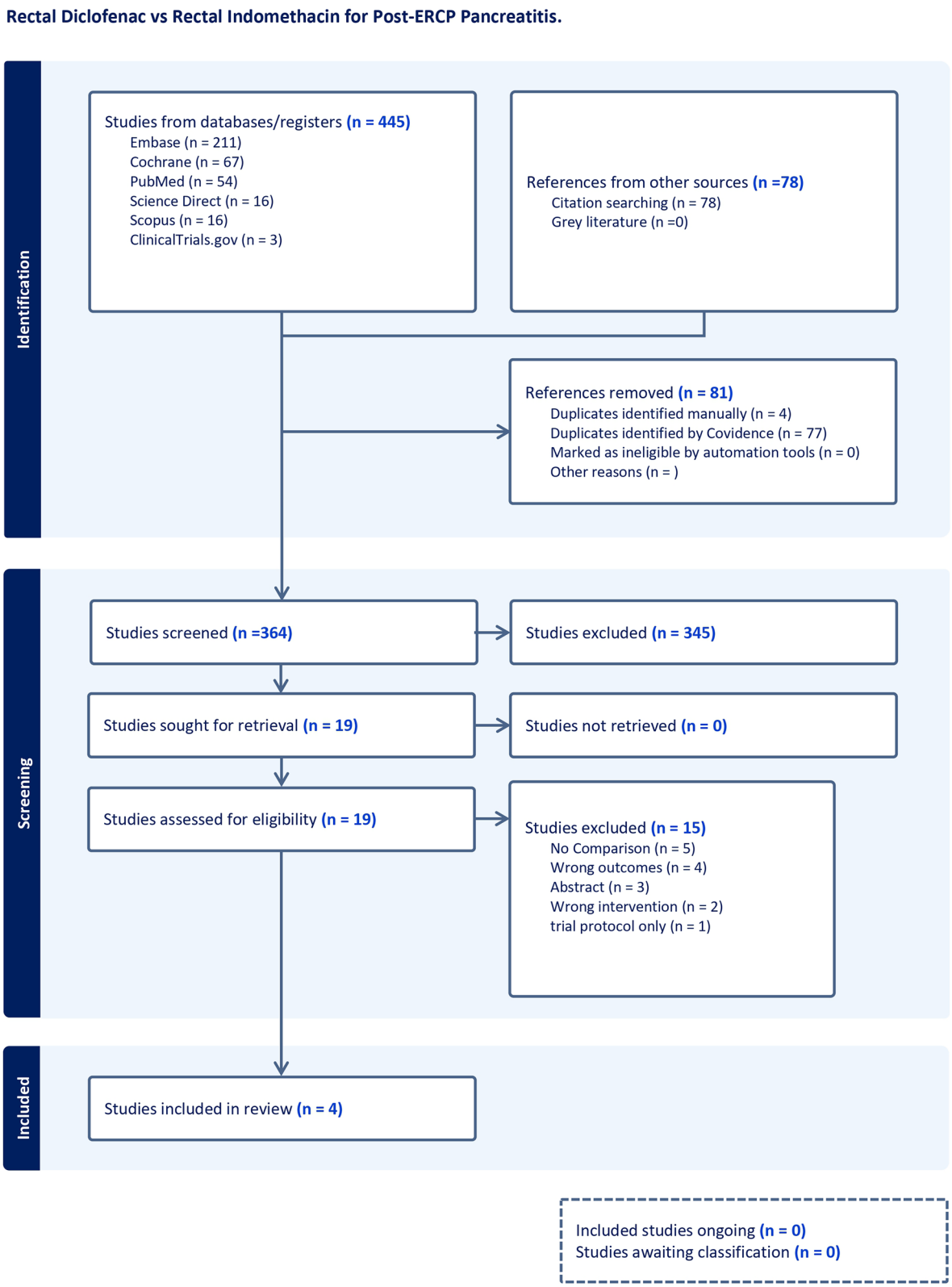

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing the study screening and selection Process

Table 1 Baseline characteristics of included studies and study populations

Baseline study and patient characteristics									
Study name	Country	Study Design	Intervention	Control	Sample Size	Mean age (years)	Male – n (%)	Dosage (mg)	Outcomes (n)*
Alizadeha AH et al., 2016	Iran	Randomized clinical trial	Diclofenac	Indomethacin	124/122	56.5 ± 18.7/58.0 ± 16.8	58/57	100/100	5
Janssens LP et al., 2024	USA	Retrospective cohort	Diclofenac	Indomethacin	304/728	57.2 ± 17.3 / 56.1 ± 17	139/330	100 /100	4
Wu X et al., 2025	China	Randomized clinical trial	Diclofenac	Indomethacin[a]	247/188	–/–	126/91	75/100	9
Kang X et al., 2025	China	Randomized clinical trial	Diclofenac	Indomethacin	587/592	61/61	321/314	Two 50 suppositories / Two 50 suppositories	9

Data are consistently presented in the format of intervention/control (diclofenac/indomethacin)

*Number of meta-analyzed primary and secondary outcomes contributed by each study

aThe control group was consistent across all included studies, except for Wu X et al., which included an additional combined therapy arm receiving both indomethacin and diclofenac

pancreatitis (RR 1.00, 95% CI 0.86–1.18; p = 0.97). Regarding procedure-related factors, no significant differences were observed between the groups in terms of sphincterotomy (RR 0.95, 95% CI 0.79–1.15; p = 0.60), pancreatic duct stenting (RR 0.86, 95% CI 0.70–1.04; p = 0.11), cannulation of the pancreatic duct (RR 1.25, 95% CI 0.74–2.10; p = 0.40), or precut sphincterotomy (RR 1.09, 95% CI 0.62–1.92; p = 0.77). Exclusion of Kang X et al. (2025) [11] in the sphincterotomy analysis reduced heterogeneity to 48%, while exclusion of Alizadeh AH et al. (2017) [10] in the precut sphincterotomy analysis reduced heterogeneity to 0% and produced a significant pooled estimate of 6.89 (95% CI: 2.11–22.49). However, balloon dilatation was significantly less frequent in the diclofenac group (RR 0.78, 95% CI 0.68–0.89; p < 0.0003), representing the only procedure-related factor with a statistically significant imbalance. For operator-related factors, trainee involvement was comparable between groups (RR 1.21, 95% CI 0.91–1.60; p = 0.18). Lastly, under indications for ERCP, there were no significant differences in biliary indications (RR 1.03, 95% CI 1.00–1.07; p = 0.06), pancreatic indications (RR 0.91, 95% CI 0.75–1.10; p > 0.05), or other indications (p = 0.52) Table 3.

Primary and Secondary Outcome

The primary outcomes analysis for PEP did not show any statistically significant difference between diclofenac and indomethacin in various severity groups. Mild PEP did not show a significant difference (RR 1.24, 95% CI 0.94–1.63; p = 0.13; $I^2 = 0\%$). Subgroup analyses based on the Cotton criteria and the revised Atlanta classification did not reveal any statistically significant differences (Supplementary Figure S3). Moderate-to-mild PEP showed equal rates (RR 0.60, 95% CI 0.21–1.73; p = 0.34; $I^2 = 0\%$). Severe PEP also did not show a significant difference (RR 1.09, 95% CI 0.32–3.77; p = 0.89; $I^2 = 1\%$), with unremarkable subgroup differences (Supplementary Figure S4). The pooling of the estimate for moderate-to-severe PEP was also not significant (RR 0.97, 95% CI 0.46–2.05; p = 0.94). Similarly, for overall PEP across the four included studies and across all severity levels, neither diclofenac nor indomethacin demonstrated superiority in prevention (RR 1.17, 95% CI 0.92–1.49; p = 0.20). The fixed-effects model appeared robust, with no evidence of sampling bias, as reflected by the low heterogeneity ($I^2 = 0\%$) (Fig. 2). These results demonstrate the similar efficacy of diclofenac and indomethacin in preventing PEP at all levels of severity. Subgroup analyses from RCTs and observational studies did not reveal any significant differences Table 4.

Our analysis of adverse events demonstrated that diclofenac and indomethacin had comparable safety profiles. There were no significant differences in mortality or any specific complication. A non-significant trend favoring indomethacin was observed in overall complications (RR 1.26, 95% CI 0.99–1.61; p = 0.65; $I^2 = 0\%$). Several

Table 2 GRADE assessment of certainty of evidence for each outcome

GRADE (Grading of recommendations, assessment, development and evaluations) assessment					
Outcome	No. of participants	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		COE
			Risk difference	95% CI	
Primary outcomes					
Overall PEP	2917 (4 studies)	1.17 [0.92; 1.49]	10 more per 1000	from 8 fewer to 34 more per 1000	⨁⨁⨁⊖ Moderate[a]
Mild PEP	2917 (4 studies)	1.24 [0.94; 1.63]	15.1 more per 1000	from 3.8 fewer to 39.4 more per 1000	⨁⨁⨁⊖ Moderate[b]
Moderate to mild PEP	681 (2 studies)	0.60 [0.21; 1.72]	4.3 fewer per 1000	from 8.6 more to 8.5 fewer per 1000	⨁⨁⊖⊖ Low[c]
Severe PEP	1713 (3 studies)	1.09 [0.32; 3.77]	0.5 more per 1000	from 3.9 fewer to 16.0 more per 1000	⨁⨁⊖⊖ Low[d]
Moderate to severe PEP	2236 (2 studies)	0.97 [0.46;2.05]	0.2 fewer per 1000	from 3.6 fewer to 7.1 more per 1000	⨁⨁⊖⊖ Low[e]
Secondary outcomes					
Mortality	1450 (2 studies)	1.0 [0.27;3.68]	0.0 more per 1,000	from 2.0 fewer to 7.4 more per 1000	⨁⨁⊖⊖ Low[f]
Bleeding	1639 (2 studies)	1.14 [0.60; 2.16]	1.5 more per 1000	from 2.9 fewer to 6.7 more per 1000	⨁⨁⨁⊖ Moderate[g]
Biliary tract infection	1639 (2 studies)	0.95 [0.51; 1.78]	1.1 fewer per 1000	from 6.4 fewer to 8.3 more per 1000	⨁⨁⨁⊖ Moderate[h]
Perforation	1639 (2 studies)	1.17 [0.37; 3.69]	1.4 more per 1000	from 3.6 fewer to 9.1 more per 1000	⨁⨁⊖⊖ Low[i]
Overall complications	1639 (2 studies)	1.26 [0.99; 1.61]	30.5 more per 1000	from 1.5 fewer to 73.0 more per 1000	⨁⨁⨁⊖ Moderate[j]
Other complications	1639 (2 studies)	1.11 [0.73; 1.67]	5.8 more per 1000	from 9.4 fewer to 29.4 more per 1000	⨁⨁⨁⊖ Moderate[k]

Note: The GRADE Working Group grades of evidence were as follows: High certainty: "We are very confident that the true effect lies close to that of the estimate of the effect"; Moderate certainty: "We are moderately confident in the estimate of the effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different"; Low certainty: "Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect"; Very low certainty: "We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect."

COE certainty of evidence, *CI* confidence interval, *GRADE* grading of recommendations assessment development and evaluation, *PEP* post-ERCP pancreatitis, *ERCP* endoscopic retrograde cholangiopancreatography

[a]The certainty of evidence is downgraded by one level for imprecision due to a wide 95% CI that crosses the line of no effect and includes clinically non-negligible benefit and harm. All other domains are sound. [b]The certainty of evidence is downgraded by one level for imprecision due to a wide 95% CI that crosses the line of no effect and includes clinically non-negligible benefit and harm. [c]The certainty of evidence was downgraded by two levels due to very serious imprecision. Despite low risk of bias and no heterogeneity, the total number of events was very low, and the 95% CI (RR 0.60, 0.21–1.73) was wide, crossing the line of no effect and including both meaningful benefit and harm. [d]The certainty of evidence was downgraded for very serious imprecision due to extremely wide confidence interval and very low number of events, despite low heterogeneity and risk of bias. [e]The certainty of evidence was downgraded two levels for very serious imprecision with a wide CI spanning important benefit and harm (RR 0.97, 95% CI 0.46–2.05). [f]The certainty of evidence was downgraded by two levels for very serious imprecision due to extremely low event count and wide confidence interval that spans both substantial harm and benefit. [g]The certainty of evidence was downgraded due to serious imprecision. Although both studies had low risk of bias and there was no heterogeneity ($I^2 = 0\%$), the total number of events was low ($n = 38$), and the confidence interval (RR 1.14, 95% CI: 0.60–2.15) was wide and included both meaningful benefit and harm. [h]The certainty of evidence was downgraded for serious imprecision due to low event rate and wide confidence interval (RR 0.51–1.78) that spans both benefit and harm. [i]The certainty of evidence was downgraded for very serious imprecision due to a low number of events and a wide confidence interval (RR 0.37–3.69) that includes both substantial harm and benefit. [j]The certainty of evidence was downgraded for serious imprecision as the confidence interval (RR 0.99–1.60) includes the possibility of no effect despite a large sample size and consistent direction of effect. [k]The certainty of evidence was downgraded for serious imprecision due to a wide confidence interval (RR 0.73–1.67) that includes both meaningful benefit and harm, despite consistent results

specific complications were similar: perforation (RR 1.17, 95% CI 0.37–3.69; $p = 0.79$; $I^2 = 0\%$), biliary tract infection (RR 0.95, 95% CI 0.51–1.78; $p = 0.87$; $I^2 = 0\%$), bleeding (RR 1.14, 95% CI 0.60–2.16; $p = 0.69$; $I^2 = 0\%$), and other complications (RR 1.10, 95% CI 0.73–1.67; $p = 0.65$; $I^2 = 0\%$). The mortality rates were similar between the groups (RR 1.00, 95% CI 0.27–3.68; $p = 0.13$; $I^2 = 0\%$). There were no clinically significant variations in safety

Table 3 Baseline procedural characteristics, with categorization into patient-related factors, procedure-related factors, operator-related factors, and indications for ERCP

Table of baseline procedural details						
	Study count	Estimate	Model*	P-value	Heterogeneity (I^2%)	Tau^2
Patient-related risk factors						
Hx of pancreatitis	3	1.00 [0.86; 1.18]	Fixed effect	0.97	0%	0.00
Procedure-related factors						
Sphincteromy	3	0.95 [0.79; 1.15]	Random effect	0.60	83%	0.02
Pancreatic duct stenting	2	0.85 [0.70; 1.03]	Fixed effect	0.10	0%	–
Cannulation of pancreatic duct	4	1.25 [0.74, 2.10]	Random effect	0.40	93%	0.24
Balloon dilatation	3	0.78 (0.68, 0.89]	Fixed effect	0.0003	0%	–
Precut sphincterotomy	3	1.09 [0.62, 1.92]	Random effect	0.77	86%	0.18
Operator-related factors						
Trainee involvement	2	1.21 [0.91; 1.60]	Random effect	0.18	88%	0.04
Indication of ERCP						
Biliary indication of ERCP	3	1.03 [1.00, 1.07]	Fixed effect	0.06	16%	–
Pancreatic indication of ERCP	3	0.91 [0.75, 1.10]	Fixed effect	0.33	0%	–
Other indication	2	0.84 [0.51, 1.41]	Random effect	0.52	67%	0.09

Hx history, *ERCP*, endoscopic retrograde cholangiopancreatography

Model*: The choice of meta-analytic model was based on the degree of heterogeneity. A fixed-effect model was used when $I2 < 50\%$, indicating low heterogeneity, whereas a random-effects model was applied when $I2 \geq 50\%$, reflecting substantial heterogeneity

This meta-analysis abided by the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines. A comprehensive literature search and independent screening process were used to minimize selection bias. Of these, 4 studies—comprising 3 randomized controlled trials (RCTs)—met all inclusion criteria. The pooled analysis included a non-overlapping population of 2917 patients

Fig. 2 Forest plot comparing rectal diclofenac and indomethacin for the prevention of overall post ERCP pancreatitis. *ERCP* endoscopic retrograde cholangiopancreatography, M-H: Mantel–Haenszel

profiles, as evidenced by the low heterogeneity ($I^2 = 0\%$) and confidence intervals that crossed unity for all secondary outcomes. Subgroup analyses (RCTs and observational studies) showed no significant differences.

Assessment of Publication Bias

Due to the limited number of included studies (n = 4), formal assessments of small-study effects, including funnel plot visualization and Egger's regression test, were not performed, in line with recommended methodological standards.

Discussion

Our systematic review and meta-analysis, the first to directly compare rectal diclofenac to indomethacin for preventing PEP, found no statistically significant difference in efficacy or safety between the two agents. Our analysis of four studies, including 2,917 patients, demonstrated that the incidence of overall PEP was comparable between groups (RR 1.17, 95% CI 0.92–1.49) with neither diclofenac nor indomethacin showing superiority over each other. This equivalence persisted across all PEP severities and for secondary outcomes like all-cause

Table 4 Outcomes categorized as primary and secondary endpoints

Table of outcomes						
	Study count	Estimate	Model*	P-value	Hetero-geneity (I^2%)	Tau^2
Primary outcomes						
Mild PEP	4	1.24 [0.94; 1.63]	fixed-effect	0.13	0%	
Moderate-to-mild PEP	2	0.60 [0.21; 1.72]	fixed-effect	0.34	0%	–
Moderate-to-severe PEP	2	0.97 [0.46; 2.05]	fixed-effect	0.94	0%	–
Severe PEP	3	1.09 [0.32; 3.77]	fixed-effect	0.89	1%	–
Overall PEP	4	1.17 [0.92; 1.49]	fixed-effect	0.20	0%	0
Secondary outcomes						
Mortality	2	1.00 [0.27, 3.68]	fixed-effect	0.95	0%	–
Bleeding	2	1.14 [0.60; 2.16]	fixed-effect	0.69	0%	–
Biliary tract infection	2	0.95 [0.51; 1.78]	fixed-effect	0.87	0%	–
Perforation	2	1.17 [0.37; 3.69]	fixed-effect	0.79	0%	–
Overall complications	2	1.26 [0.99; 1.61]	fixed-effect	0.06	0%	–
Other complications	2	1.10 [0.73; 1.67]	fixed-effect	0.65	0%	–

PEP post-ERCP pancreatitis, *ERCP* endoscopic retrograde cholangiopancreatography

Model*: The choice of meta-analytic model was based on the degree of heterogeneity. A fixed-effect model was used when $I2 < 50\%$, indicating low heterogeneity, whereas a random-effects model was applied when $I2 \geq 50\%$, reflecting substantial heterogeneity

This meta-analysis abided by the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines. A comprehensive literature search and independent screening process were used to minimize selection bias. of these, 4 studies—comprising 3 randomized controlled trials (RCTs)—met all inclusion criteria. The pooled analysis included a non-overlapping population of 2917 patients

mortality, bleeding, perforation, and biliary tract infections. All pooled outcomes showed negligible heterogeneity ($I^2 = 0\%$), indicating high consistency across the included studies.

Our direct-comparison findings of therapeutic equivalence align remarkably well with several previous meta-analyses that indirectly compared the two agents. For example, reviews by Yu et al. (2021), Patai et al. (2017), and Sethi et al. (2014) all concluded that the efficacy of indomethacin and diclofenac was similar [16–18]. Both diclofenac and indomethacin inhibit cyclooxygenase and phospholipase A2, which are the key pathways in PEP [19]. Diclofenac has 50–60% oral bioavailability due to first-pass metabolism, whereas indomethacin approaches 100% [20, 21]. Rectal administration minimizes these differences by bypassing first-pass metabolism [22]. A 2025 study by Swaminathan et al. [13] showed that rectal diclofenac achieves sustained systemic exposure and pancreatic penetration, resulting in similar tissue distribution and concentration as indomethacin. This explains their comparable efficacy and safety.

A meta-analysis by Hou et al. (2017) indicated that diclofenac (RR 0.41; 95% CI: 0.19–0.90) was probably superior to indomethacin (RR 0.58; 95% CI: 0.45–0.75) [23] in preventing PEP. However, this finding was based on indirect comparisons rather than head-to-head trials. Meta-analyses conducted by Sethi et al. (2014) and Patai A et al. (2017) were also based on indirect comparisons but revealed no superiority of either diclofenac nor indomethacin based on testing for subgroup differences [17, 18]. As such, the ambiguity largely persisted due to the lack of head-to-head trials. Our meta-analysis confirms earlier results but is based on a more robust and specific set of inclusion criteria. Similar to Patai A et al. (2017), our work confirms that no NSAID is superior overall, nor across PEP severity levels. A recent network meta-analysis on optimal strategies for preventing PEP showed diclofenac plus lactated Ringer's solution as one of the most effective preventive methods for patients at average risk [5]. This apparent inconsistency with our findings may be due to the comparison of the effects of combination therapies with those of monotherapy. Lastly, certain pharmacokinetic studies have suggested theoretical advantages for one medication over another. Some analyses have highlighted diclofenac's faster absorption profile and indomethacin's longer half-life as potentially clinically relevant differences.

These apparent contradictions may be due to several methodological factors in earlier research, including a reliance on indirect comparisons resulting from the limited availability of head-to-head trials. Indirect comparisons, while methodologically sound, can introduce additional uncertainty and may not capture the nuanced differences that emerge in direct comparative studies., Other factors

include heterogeneity in study populations and PEP definitions, insufficient statistical power to rule out minor differences, and potential publication bias. Our analysis, which benefits from direct head-to-head evidence from recent, methodologically rigorous trials, such as the 2025 DIPPP study, helps resolve these prior inconsistencies [11]. These findings have significant implications for clinical practice and the development of guidelines. Major society guidelines recommend rectal NSAIDs; however, no drug is given preference over another. The European Society of Gastrointestinal Endoscopy (ESGE) advises that all patients without contraindications should take 100 mg of either indomethacin or diclofenac either before or after ERCP, based on moderate-quality evidence [24]. This also supports recommendations from the American Society for Gastrointestinal Endoscopy (ASGE) to use either NSAID in both unselected and high-risk patients (moderate quality of evidence), as well as Japanese guidelines that support rectal NSAIDs as a key preventive measure alongside pancreatic duct stenting [25, 26]. Moderate quality of evidence indicates that "Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate [25].

Ultimately, our analysis provides high-quality evidence that the choice between these two recommended NSAIDs can be guided by factors like cost and availability, rather than differences in efficacy. From a healthcare policy perspective, this is important. A Mayo Clinic study, for example, showed annual cost savings ($441,460.62) by switching from indomethacin to compounded diclofenac, with identical clinical outcomes [12, 15]. Our analysis provides the clinical evidence base to support such cost-driven decisions globally.

The strengths of this review include its focused research question, comprehensive search strategy, rigorous methodology with GRADE assessment, and the resulting negligible heterogeneity across all outcomes. However, our analysis also has some limitations. First, the relatively small number of available randomized comparative trials (n = 4) limits the scope of this analysis and precludes formal subgroup evaluation or assessment of publication bias. Nonetheless, the aggregate sample size was substantial (n = 2,917). Second, cost-effectiveness outcomes were not consistently reported, restricting the ability to perform a formal economic analysis. However, drug acquisition costs can be readily assessed within local health care contexts to inform decision-making. Finally, there was a baseline imbalance in the use of balloon dilatation of the native papilla, which occurred less frequently in the diclofenac group ($P < 0.001$). This factor may represent a potential confounder, underscoring the importance of stratification or adjustment for this variable in future studies.

Our study also identifies several future research avenues. Large-scale pragmatic trials are necessary to assess the real-world cost-effectiveness across diverse healthcare systems. Further pharmacokinetic and pharmacodynamic studies, such as the recent work by Swaminathan et al., provide a starting point; however, more research is needed to understand tissue-specific drug distribution and the duration of anti-inflammatory effects [13]. These investigations may determine the best timing and dosage. Based on this established efficacy, research should also explore synergistic combination prevention strategies, novel delivery systems, and personalized medicine approaches based on pharmacogenomics. Lastly, new surveys indicate inadequate adoption of NSAID prophylaxis despite solid evidence and guidelines; more research into implementation strategies may enhance clinical outcomes [27].

Conclusion

Rectal diclofenac and indomethacin demonstrate equivalent efficacy and safety for PEP prevention across all severity grades, with no meaningful differences in secondary outcomes. Given this equivalence, selection between these guideline-recommended NSAIDs may be driven by cost, availability, and formulary considerations rather than therapeutic performance.

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Data Availability Data are available from the corresponding author upon reasonable request.

Declarations

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Ethical consideration This investigation is a meta-analysis that utilizes data extracted from previously published studies and does not involve direct interaction with human or animal subjects; accordingly, institutional review board approval was not applicable. All included studies reported compliance with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. All authors have reviewed and approved the final manuscript and consent to its publication.

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