Med Glas (Zenica) 2026;23(1)
https://doi.org/10.17392/2062-23-01

Med Glas (Zenica)

ORIGINAL ARTICLE

Prophylactic use of rectal diclofenac in mitigating post-endoscopic retrograde cholangiopancreatography pancreatitis risk and severity: low- vs high-dose efficacy and timing strategies— a meta-analysis

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ABSTRACT

Aim Post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most prevalent adverse event with significant morbidity following ERCP. Several guidelines have suggested the use of rectal diclofenac as a promising option to prevent PEP. Nonetheless, the recommended optimal dose and timing of administration remain unclear. The aim of this study was to evaluate the efficacy of different doses and timing of rectal diclofenac administration in preventing PEP.

Methods Literature search was conducted on 3 databases: PubMed/MEDLINE, Cochrane Library, and ScienceDirect. The included studies were evaluated for the method and reported data quality. Data were summarized, and statistical analyses were performed using RevMan 5.4.1 software.

Results Thirteen eligible studies with a total of 8602 patients undergoing ERCP were included. A significantly lower moderate-severe PEP prevalence in patients treated with rectal diclofenac compared to control (RR 0.67; 95% CI: 0.51-0.89; p=0.006) was found. High-dose rectal diclofenac significantly reduced the prevalence of moderate to severe PEP (RR 0.63; 95% CI: 0.450.89; p=0.008). Administering rectal diclofenac before procedure significantly lowered the prevalence of moderate to severe PEP (RR 0.66; 95% CI: 0.47-0.92; p=0.01). Adverse events related to ERCP procedure were comparable in both groups. No adverse event related to rectal diclofenac administration was reported across all studies.

Conclusion High-dose rectal diclofenac administered before ERCP procedure is effective in reducing the prevalence and severity of PEP, and is well tolerated with favourable safety profile.

Keywords: anti-inflammatory agents, non-steroids, pancreatitis, prevention, suppository

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an interventional procedure that involves upper gastrointestinal endoscopy and x-rays, indicated for the diagnosis and management of hepatobiliary and pancreatic system disorders (1). The prevalent adverse event following this extensively utilized procedure is acute pancreatitis. Post-ERCP acute pancreatitis (PEP) is common, occurring in 3 - 10% of patients, and is frequently linked to considerable morbidity and mortality (2). Therefore, the implementation of adequate prophylactic measures is crucial to avoid the development of PEP.

Current strategies for preventing post-ERCP pancreatitis (PEP) include pancreatic duct stent placement and the use of medications. However, most pharmacological agents, for instance nitroglycerine, somatostatin, and octreotide, assessed in clinical trials have shown limited effectiveness against PEP prevention (3). Several guidelines have suggested the use of rectal diclofenac as a promising option to prevent PEP (4-7). Despite this, the recommended optimal dose and timing of administration in relation to the ERCP procedure remain unclear. The European Society of Gastrointestinal Endoscopy (ESGE) recommends administering a high-dose (100 mg) rectal diclofenac before ERCP procedure (6). The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JHBPS) recommends a low-dose (25–50 mg) rectal diclofenac administered immediately after the ERCP procedure (7). Thus, it remains controversial whether rectal diclofenac effectively reduces the incidence and severity of PEP.

The aim of this study was to assess the efficacy of 100 mg vs 25–50 mg of rectal diclofenac, administered before vs after ERCP procedure in preventing PEP compared to a control group of patients without any prophylaxes.

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| Submitted: 07. Aug 2025. Revised: 22. Nov 2025, Accepted: 27. Nov 2025.

MATERIALS AND METHODS

Materials and study design

This systematic review was done by conducting comprehensive literature search on three databases: PubMed/MEDLINE, ScienceDirect, and the Cochrane Library, to identify studies up to 2025. The keywords "rectal diclofenac", "pancreatitis", and "prophylaxis" were utilized for literature search. The keywords were entered into the advanced search forms of the databases, incorporating the Boolean operator 'OR' to obtain synonym results in accordance with the MeSH Term. Concurrently, the Boolean operator 'AND' was applied to the keywords between each term to yield results that encompass all specified keywords. The search terms were used as follows: ("rectal diclofenac" OR "diclofenac" OR "nsaid") AND ("post-ERCP pancreatitis" OR "pancreatitis" OR "endoscopic retrograde cholangiopancreatography" "ERCP") AND ("prophylaxis" OR "prevention").

The eligibility criteria included studies with a population of patients undergoing ERCP who received rectal diclofenac as the intervention and had a control group receiving either no treatment or a placebo as comparison. The studies must have reported outcomes including prevalence and severity of PEP as primary endpoint, alongside adverse events to assess the safety profile. Eligible studies were required to be published in English with full-text access available.

The excluded studies comprised those that included participants younger than 18 years of age, pregnant and/or lactating women, patients undergoing ERCP for biliary stent removal, or studies with NSAIDs as additional therapy to other preventions. Studies with insufficient data such as missing baseline or follow-up numerical data were excluded, as were animal studies, reviews, case reports, editorials, and duplicates.

The protocol for this review was registered on 18 June 2025 with the International Prospective Register of Systematic Reviews (PROSPERO) under identification number CRD420251076066.

Methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). After comprehensive search was completed, duplicates were removed. The identified studies were screened based on title and abstract manually by two independent authors (ML and PL). Each article deemed relevant and within the scope of this systematic review by at least one author was selected for further evaluation. Each author would review the selected studies that passed the initial screening for their eligibility. Disagreements between authors were reviewed and settled by a third author (TS). Each accessible full-text article was independently rated by two authors. Third author's opinion settled the disagreement between authors' judgements.

The studies that fulfilled the inclusion criteria were analysed. Data extracted from the studies included the following: the name of the first author, year and site of publication, sample sizes, inclusion and exclusion criteria, number of patients treated with rectal diclofenac or assigned to the control group, patient outcomes for both groups, and baseline characteristics of the samples. The primary outcome was the prevalence of post-ERCP pancreatitis (PEP), defined as abdominal pain accompanied by a serum amylase level ≥3 times the normal value within 24 hours after ERCP (9). The second outcomes anticipated were the severity of PEP classified using the Revised Atlanta Classification (RAC) as mild (needed 2 - 3 days of hospital stay), moderate (needed 4 - 10 days of hospital stay), or severe PEP (needed > 10 days of hospital stay) (10); and adverse events.

Statistical analyses

The Cochrane risk of bias 2.0 tool (RoB-2) was utilized to assess the quality of the included randomized controlled trials. The tool is structured into five domains through which bias might be categorized as 'low risk', 'high risk', or 'some concerns' of bias (11). The Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) were used to assess all included non-randomized studies (12).

The statistical analyses were carried out utilizing RevMan 5.4.1 software. Outcomes of the studies were pooled as prevalence with 95% confidence intervals (CI). Subgroup analyses were performed to investigate the variability among trials regarding various rectal diclofenac doses and timing of administration. Risk ratio (RR) was used to compare the probability of an event occurring in the intervention group to that in the control group across studies. The I^2 statistic was used to determine the degree of heterogeneity among the studies included in this meta-analysis (13). The I^2 value indicates the percentage of variability attributable to differences in study populations, interventions, methodologies, or outcome measurements (14). The outcomes with $p<0.05$ were considered to have statistical significance.

RESULTS

PRISMA flowchart diagram (Figure 1) depicted the study selection process. After completed search in 3 scientific databases, a total of 963 studies were obtained: 510 from ScienceDirect, 317 from PubMed, and 136 from the Cochrane Library. Forty-eight duplicates were identified and removed, resulting in 915 studies for screening. After screening the remaining studies, 868 were excluded for not meeting the inclusion criteria, having irrelevant titles, containing inappropriate abstracts, and being published in languages other than English. The final 47 studies were assessed for eligibility, and only 36 were

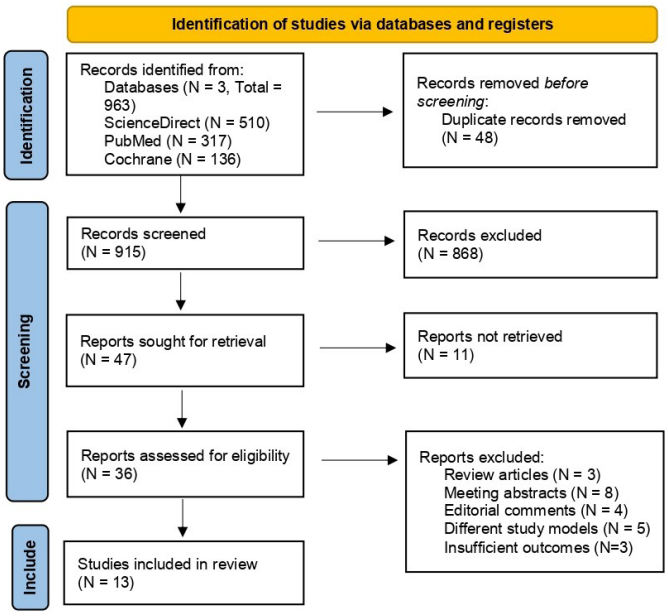

Figure 1. PRISMA flowchart

Table 1. Baseline demographic and clinical characteristics of the studies

Authors, Year, Country	Sample size	Baseline characteristics of participants				Rectal Diclofenac	
		Age (mean±SD) (years)	Sex, F/M (N)	BMI (mean±SD)	History of pancreatitis (N)	Dosage	Timing
Sakai et al., 2023 (15) Japan	Total = 367 D=187 C=180	D: 74.8±12.3 C: 74.8±13.0	D: 80/107 C: 84/96	D: 22.1±3.6 C: 21.9±3.9	D: 1 C: 2	25 – 50 mg	30 min before ERCP
Maeda et al., 2021 (16) Japan	Total =276 D=83 C=193	D: 84±2 C: 82±2.25	D: 49/34 C: 113/80	D: 22±0.75 C: 22±1.25	D: 4 C: 3	25 mg	30 min before ERCP
Takaori et al., 2021 (17) Japan	Total = 515 D=246 C=269	N/I	D: 104/142 C: 101/168	N/I	D: 7 C: 12	25 – 50 mg	30 min before ERCP
Tomoda et al., 2021 (18) Japan	Total =132 D=66 C=66	D: 74 ± 4.5 C: 70±3.75	D: 54/12 C: 56/10	N/I	D: 1 C: 7	25 – 50 mg	before ERCP
Katoh et al., 2020 (19) Japan	Total=297 D=147 C=150	D: 74.3±11.8 C: 74.0±12.7	D: 65/82 C: 55/95	N/I	D: 8 C: 8	25 – 50 mg	30 min before ERCP
Koskensalo et al., 2020 (20) Finland	Total=2000 D=1000 C=1000	D: 40± 14.25 C: 39±15.75	D: 370/630 C: 401/591	D: 25.0±7.83 C: 24.5±8.98	N/I	100 mg	before ERCP
Geraci et al., 2019 (21) Italy	Total=40 D=20 C=20	D: 59.8±5.25 C: 58.6±4.25	D: 12/8 C: 9/11	N/I	D: 0 C: 0	100 mg	30-60 min before ERCP
Del-Olmo-Martínez et al., 2018 (22) Spain	Total = 1512 D=794 C=718	D: 72.9 ± 13.7 C: 73.1±14.23	D: 347/447 C: 348/370	N/I	D: 31 C: 40	100 mg	before ERCP
Okuno et al., 2018 (23) Japan	Total=147 D=74 C=73	D: 78±11.75 C: 83±13.25	D: 39/35 C: 37/36	D: 21.5±5.1 C: 20.0±4.6	N/I	25 mg	30 min before ERCP
Rainio et al., 2017 (24) Finland	Total=2000 D=1000 C=1000	D: 64±19.75 C: 63±20.5	D: 430/570 C: 421/579	D: 24.8±10.9 C: 24.8±10.85	D: 142 C: 137	100 mg	before ERCP
Leerhøy et al., 2016 (25) Denmark	Total=772 D =378 C =394	D: 65±18 C: 66±19	D: 216/162 C: 249/145	D: 26±5 C: 26±6	N/I	100 mg	after ERCP
Patil et al., 2016 (26) India	Total=400 D =200 C =200	N/I	D: 128/72 C: 123/77	N/I	D: 40 C: 35	100 mg	before ERCP
Lua et al., 2015 (27) Malaysia	Total = 144 D=69 C=75	D: 50.3±17.6 C: 49.6±16.8	D: 35/34 C: 50/25	N/I	D: 1 C: 0	100 mg	after ERCP

BMI, body mass index; C, control group; D, rectal diclofenac group; F, female; M, male; N, number; N/I, no information; ERCP, endoscopic retrograde cholangiopancreatography

successfully retrieved for full-text. Of these studies, 23 were excluded: 3 were reviews, 8 were meeting abstracts, 4 were editorial commentaries, 5 used different study models, and 3 had insufficient outcome data. Thus, the remaining 13 studies that met the inclusion criteria were included in the meta-analysis.

Among the 13 studies included in the analysis, four were randomized controlled trials (RCTs). The quality assessment using ROB-2 should be mentioned in the statistical analysis indicating that all RCTs studies were regarded to have low risk of bias (Figure 2A). Other 9 non-randomized studies were evaluated for quality with ROBINS-I should be mentioned in the statistical analysis. Of those, three studies were regarded to have moderate risk of bias, while others were regarded to have low risk of bias (Figure 2B).

The total sample size of the 13 studies was 8602 patients. The included studies were conducted in different geographic locations, ensuring less bias and a general outcome throughout distinct regions. The average age of patients was 70, ranging from 60 to 80 years of age. The proportion of female and male patients was comparable, with both comprising approximately 50%. Most patients were considered overweight with the average body mass index (BMI) of 23 kg/m2 ranging between 21 to 25 kg/m2 (Table 1).

The patients included were undergoing ERCP procedure for the first time by experienced endoscopists. The exclusion criteria applied across the studies included patients with acute or chronic pancreatitis, those with allergies or contraindications to NSAIDs (e.g., severe renal insufficiency, peptic ulcer), pregnant or breastfeeding patients or those with abnormal gastrointestinal anatomy.

Each study provided detailed information on the interventions and comparisons. In the rectal diclofenac groups, participants received either low dose rectal diclofenac (25 mg for body weight <50 kg or 50 mg for body weight > 50 kg) or high dose rectal diclofenac (100mg), administered either 30 minutes before or immediately after ERCP. The variety of doses and tim-

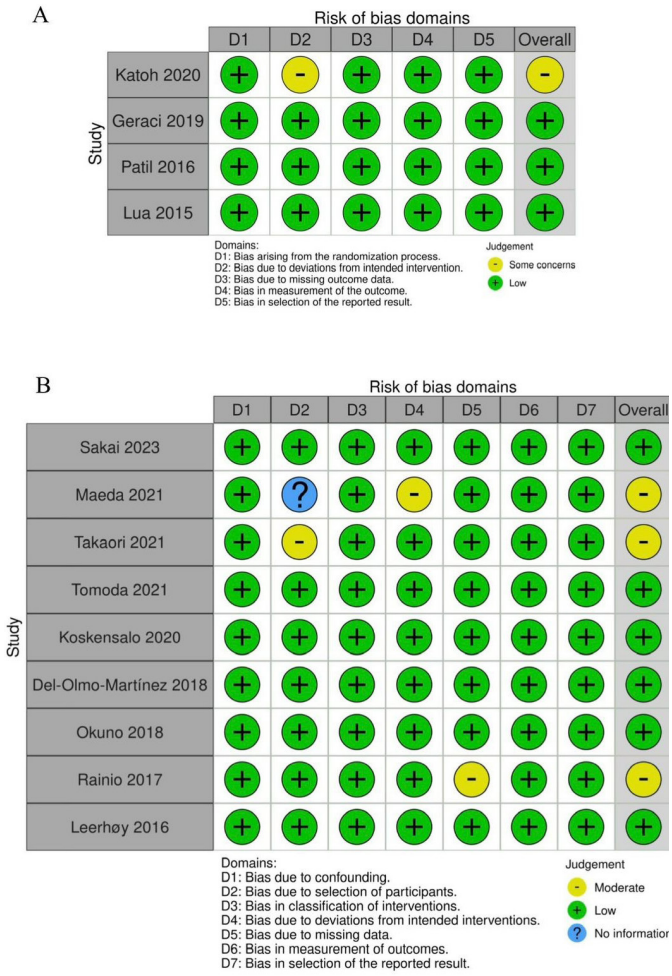

Figure 2. A) Risk of bias using Cochrane risk of bias tool for randomized trials (RoB2); B) Risk of bias using The Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I)

ing applied in this study was intended to evaluate the optimal rectal diclofenac dose and timing of administration. In the control groups, participants received no treatment for comparison. The outcome data extracted were the prevalence and severity of PEP, impact of different doses and timing for the prevalence and severity of PEP, and adverse events.

In the control group, 132 out of 4338 patients developed mild PEP, while in the rectal diclofenac group, there were only 104 out of 4262 patients who developed mild PEP. The results indicated that rectal diclofenac marginally reduced the prevalence of mild PEP compared to the control, although this finding did not demonstrate statistical significance (RR 0.82; 95% CI: 0.64-1.06; p=0.13). The prevalence of mild PEP was significantly reduced by low-dose rectal diclofenac (RR 0.56; 95% CI: 0.32-1.00; p=0.05). The use of high-dose rectal diclofenac also reduced the prevalence of mild PEP, however no statistical significance was observed (RR 0.92; 95% CI: 0.69-.22; p=0.55). The timing of rectal diclofenac administration—whether given before or after the procedure—did not show a statistically significant difference in reducing the prevalence of mild PEP. In other words, both pre-procedure and post-procedure administration of rectal diclofenac appeared to provide comparable effectiveness for preventing mild PEP (Figure 3).

The prevalence of moderate to severe PEP was significantly lower in patients treated with rectal diclofenac compared to the control (RR 0.67; 95% CI: 0.51-0.89; p=0.006). High-dose rectal diclofenac significantly decreased the prevalence of moderate to severe PEP compared to the control (RR 0.63; 95% CI: 0.45-0.89; p=0.008). Meanwhile, the effect of low-dose rectal diclofenac in this regard did not demonstrate statistical significance (RR 0.78; 95% CI: 0.46-1.31; p=0.34). The timing of rectal diclofenac administration plays a key role in preventing moderate to severe PEP. Statistical analysis showed that administering rectal diclofenac before the procedure significantly lowered the prevalence of moderate-to-severe PEP compared to the control (RR 0.66; 95% CI: 0.47-0.92; p=0.01). Conversely, the administration of rectal diclofenac after the procedure did not show a significant reduction in the prevalence of moderate to severe PEP (RR 0.71; 95% CI: 0.43-1.18; p=0.19).

In terms of adverse events, the use of rectal diclofenac reported a comparable safety profile to the control group. The occurrence of adverse events related to the ERCP procedure was comparable in the rectal diclofenac and the control group, with no statistical difference (RR 0.84; 95% CI: 0.70-1.02; p=0.08). Additionally, no adverse event was observed in the administration of rectal diclofenac across all studies.

DISCUSSION

Several studies confirmed rectal nonsteroidal anti-inflammatory drugs (NSAIDs), such as rectal diclofenac or indomethacin, to effectively prevent PEP (24,25). A systematic review and meta-analysis further evaluated the efficacy of rectal diclofenac and indomethacin, yielding that a greater number of patients developed PEP in the indomethacin group than that in the diclofenac group (26). Recent trials have evaluated rectal diclofenac as prophylactic for PEP. Studies in Europe evaluated a high dose rectal diclofenac, while studies in Asia frequently evaluated low dose rectal diclofenac, thus the results were somehow contradictory (15-17).

In this study we have evaluated the efficacy and safety of rectal diclofenac in lowering the incidence and severity of PEP, as well as focusing on the optimal dose and timing of administration. The results indicate that rectal diclofenac provided a desirable efficacy in the prevention of overall PEP prevalence, highlighting the prevalence of moderate-to-severe PEP. This result is aligned with a study which indicated that rectal diclofenac significantly decreased the prevalence of PEP, with 4.1 % of patients in the rectal diclofenac group and 13.7% of patients in the control group developing PEP (19). A study evaluating several routes of diclofenac administration demonstrated that rectal diclofenac significantly reduced the prevalence of PEP and is superior to other routes of administration (17). Regarding this result, a study indicated that rectal diclofenac lowered the incidence of PEP significantly, with the most pronounced effect observed in moderate-to-severe PEP (22). Rectal diclofenac mitigated pancreatitis pathogenesis by suppressing the inflammatory responses through the inhibition of cyclooxygenase 2-prostaglandin A2 pathway (27). Rectal administration is more effective than other routes because it allows rapid absorption and bypasses first-pass metabolism, leading to higher local concentrations and enhanced anti-inflammatory effects (28). Rectal diclofenac significantly reduces the prevalence of moderate to severe PEP, but offers minimal benefit over no treatment in mild cases. This is because it effectively disrupts the intense inflammatory cascade responsible for more severe pancreatitis. In contrary, mild pancreatitis typically results from transient enzyme leakage and minor tissue damage that is often self-limiting, which explains the lack of a significant difference in outcomes (29).

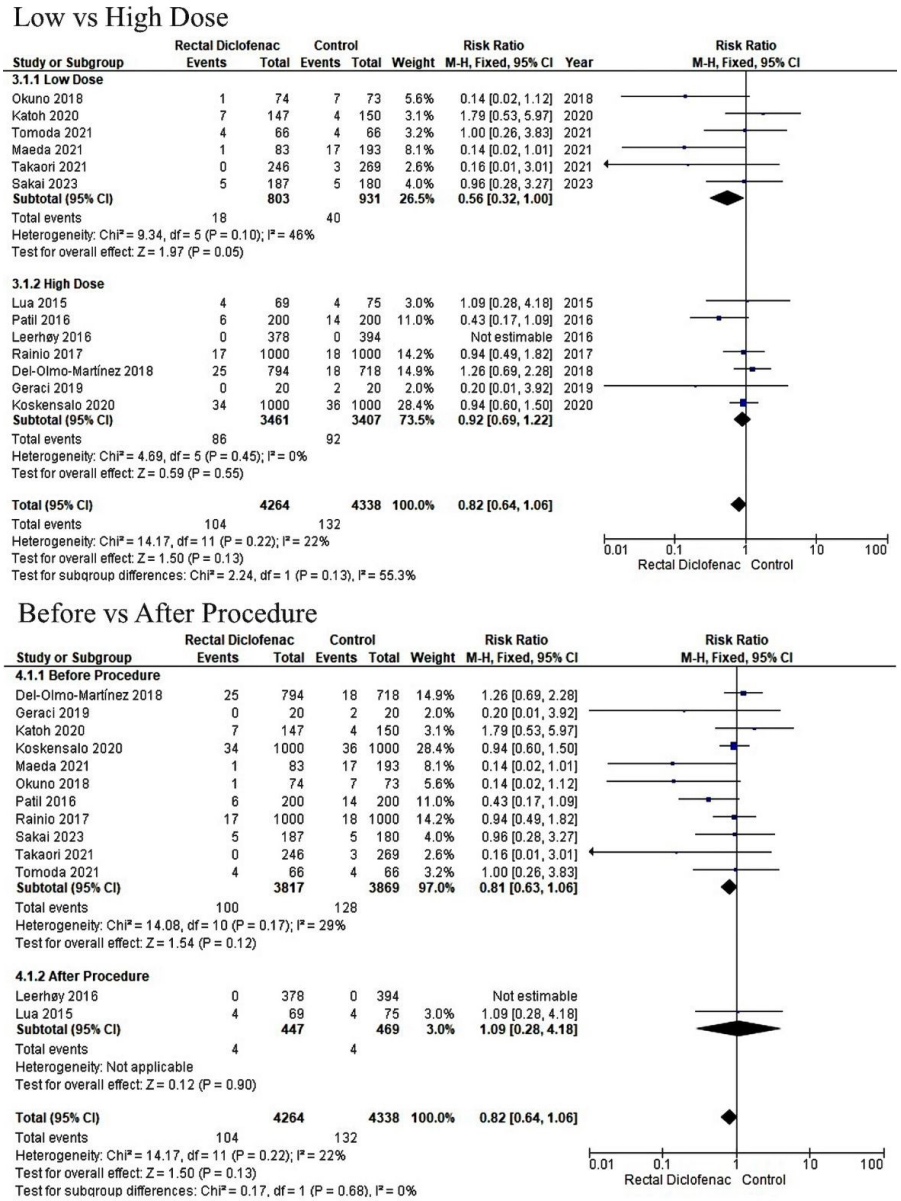

Figure 3. Forest plot of the incidence of mild post- endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) according to different doses and administration timing

This study suggested that administering a high-dose of 100 mg rectal diclofenac provided better efficacy in preventing moderate to severe PEP than low-dose rectal diclofenac and control groups. Dome studies demonstrated that prophylactic administration of 100 mg rectal diclofenac significantly reduces the prevalence of PEP up to 5% compared to the control (21). Comparing the efficacy of 25 mg versus 50 mg doses of rectal diclofenac it was found that the prevalence of PEP was significantly lower in the 50 mg group, revealing there was enhanced efficacy with a higher dose (30). A comprehensive review claimed that the efficacy of rectal diclofenac appears to be dose-dependent, with significantly reduced protection at doses lower than 50 mg. In contrast, a ceiling effect was suggested at doses above 100 mg, offering no additional benefit and potentially increasing the risk of adverse events (31).

Administering high-dose rectal diclofenac 30 minutes prior to the ERCP procedure was suggested to be more effective in preventing of moderate-to-severe PEP (17,22). This outcome was in accordance with a study by Wu et al. Reportedly, administering rectal diclofenac prior to ERCP halved the prevalence of PEP compared to administering post-ERCP, with 6.50% and 15.63% of patients developing PEP, respectively (32), additionally being associated with a shorter hospital stay (33). A study by Agahi et al. indicated that administration of rectal diclofenac both pre- and post-ERCP had no additional benefit in preventing PEP compared with pre-ERCP administration alone (34). It has been shown that pre-ERCP administration of NSAIDs ensures that therapeutic concentrations are present during the critical period of pancreatic injury and enzyme activation, thereby inhibiting the initiation and early propagation of the inflammatory cascade. Contrary, post-ERCP administration may be less effective, as the inflammatory cascade may have been already triggered, limiting its prophylactic potential (35).

Administration of rectal diclofenac showed no significantly increased risk of other adverse events related to the ERCP procedure, such as gastrointestinal (GI) bleeding, perforation, and cholangitis. No adverse event regarding the administration of rectal diclofenac was reported in this review. These findings indicate that rectal diclofenac was well tolerated, exhibiting a comparable safety profile to no treatment for patients undergoing ERCP

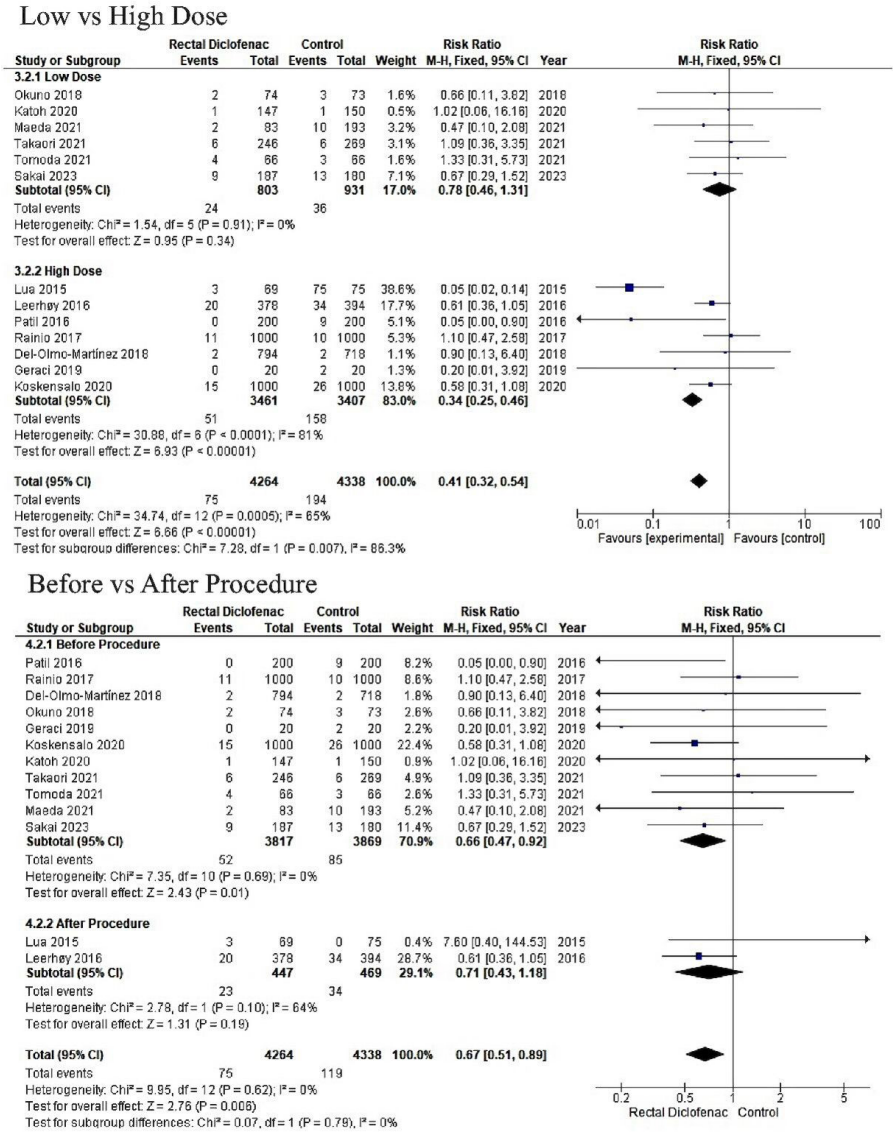

Figure 4. Forest plot of the incidence of moderate-severe post- endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) according to different doses and administration timing

procedure. Several meta-analyses concluded that rectal NSAIDs were safe and well-tolerated, with no significant side effects reported. Rectal administration enables effective local action while minimizing systemic exposure and associated side effects (29,36). Despite the encouraging outcomes reported, this study has several limitations. Firstly, the limited evaluation of confounding risk and long-term safety data may constrain the general applicability of the results reported. Secondly, the substantial heterogeneity observed across the included studies (I^2 = 65%)—particularly regarding the prevalence of moderate-to-severe PEP—indicates notable inconsistency in the reported outcomes. This variability is likely to be influenced by differences in the intervention protocols, especially the wide range of diclofenac doses (25 mg vs 100 mg) and the timing of administration (pre-ERCP vs post-ERCP). Such differences in dosing strategies may lead to variations in drug absorption and anti-inflammatory efficacy, ultimately affecting the pooled treatment effect. In addition, several potential confounders may further contribute to this heterogeneity. These include differences in baseline patient risk profiles for PEP, where known risk factors include female sex, younger age, and a history of pancreatitis or previous PEP, as well as variations in procedural complexity, such as difficult bile duct cannulation, repeated contrast injection into the pancreatic duct, and the performance of sphincterotomy. Furthermore, the use of concomitant prophylactic measures (e.g., pancreatic stents or other NSAIDs) may also influence both the incidence and severity of PEP. Collectively, these factors may partially explain the inconsistency observed across studies (37).

Future research should focus on conducting larger and multi-centred RCTs to further validate these findings and establish standardized rectal diclofenac protocols, including comparison with other preventive alternatives. We hope that by addressing these limitations, forthcoming studies may offer more reliable evidence on the use of rectal diclofenac as a prophylaxis for post-ERCP pancreatitis (PEP) in patients undergoing ERCP.

In conclusion, administering a high-dose 100 mg rectal diclofenac prior to the ERCP procedure provided a significant prophylactic efficacy against post-ERCP pancreatitis. Rectal diclofenac significantly lowered the incidence and severity of PEP. On top of that, rectal diclofenac was well-tolerated with no considerable adverse events reported. The efficacy of rectal diclofenac compared to other alternatives in preventing PEP requires further research.

AUTHOR CONTRIBUTIONS

Conceptualization, M.L. and T.S.; Methodology, M.L. and P.L; Supervision, T.S; Validation, T.S. and M.L.; Resources, P.L.; Investigation, M.L and P.L.; Formal Analysis, T.S.; Visualization, T.S. and P.L. All authors have read and agreed to the published version of the manuscript.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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