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REVIEW ARTICLE

Rectal indomethacin and diclofenac are equally efficient in preventing pancreatitis following endoscopic retrograde cholangiopancreatography in average-risk patients

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Abstract

Rectal indomethacin and diclofenac are promising drugs for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, their prophylactic effect on PEP in average-risk patients remains controversial. We performed a systematic review and meta-analysis to assess the efficacy and safety of rectal indomethacin and diclofenac in average-risk patients, and to indirectly compare the prophylactic effect of the two drugs. A comprehensive search of the PubMed, EMBASE, and Cochrane Library databases was performed to identify randomized controlled trials (RCTs) on rectal indomethacin or diclofenac for prophylaxis against PEP. Fixed- and random-effects models weighted by the Mantel–Haenszel method were used for direct comparisons. The adjusted indirect treatment comparison method was used to indirectly compare the efficacy of indomethacin and diclofenac. A total of 10 RCTs, including 2928 patients, met our inclusion criteria. No significant publication bias was identified. Pooled estimates showed that rectal indomethacin and diclofenac were associated with a significant reduction in the overall risk of PEP compared with control intervention [relative risk (RR) = 0.62; 95% confidence interval (CI): 0.46–0.83] in average-risk patients. Subgroup analyses showed that both rectal indomethacin (RR = 0.67; 95% CI: 0.49–0.94) and diclofenac (RR = 0.42; 95% CI: 0.23–0.75) were effective in the prevention of PEP. Indirect comparison showed no significant difference between the effectiveness of the two drugs in the prevention of PEP (RR = 1.607; 95% CI: 0.824–3.136). The updated meta-analysis suggests that both drugs provide equivalent protection against PEP in average-risk patients.

Introduction

As endoscopic retrograde cholangiopancreatography (ERCP) has been widely applied in the diagnosis and management of cholecystopancreatic diseases, the associated complications, especially post-ERCP pancreatitis (PEP), have received increasing attention. A systematic review of randomized controlled trials (RCTs) revealed that the overall incidence of PEP was 9.7%, and the mortality due to PEP was 0.7%.[1] Some patient- or procedure-related risk factors, such as suspected sphincter of Oddi dysfunction, female sex, previous pancreatitis, previous PEP, difficult cannulation, and pancreatic injection, have been confirmed in systemic reviews and meta-analyses.[2] Among the non-risk-stratified and high-risk RCTs, the incidence of PEP was found to be 8.5% and 14.7%, respectively.[1]

Multiple pharmacologic interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs), somatostatin and octreotide, protease inhibitors, antibiotics, trinitrin, and others, have been evaluated in clinical trials for potential efficacy in prophylaxis against PEP.[3] Among these, NSAIDs (indomethacin and diclofenac) appear to be the most promising drugs; however, only administration via the rectal route resulted in a significant benefit for the prevention of PEP compared with non-rectal administration of these drugs.[4–6] Based on previous RCTs and meta-analyses, the European Society of Gastrointestinal Endoscopy and the Japanese Society of Hepato-Biliary-Pancreatic Surgery recommended rectal administration of diclofenac or indomethacin to prevent PEP in all patients undergoing ERCP.[2,7,8] However, the guideline published by the American Society for Gastrointestinal Endoscopy in 2017 only recommended the use of rectal NSAIDs to reduce the incidence and severity of PEP in high-risk individuals, while also suggesting that rectal indomethacin may reduce the risk and severity of PEP in individuals with average risk.[9] In spite of these guidelines, surveys among endoscopists in Portugal, the United Kingdom, and the United States revealed low adoption rates of rectal NSAIDs to prevent PEP in clinical practice.[10–12]

Moreover, the prophylactic benefit of rectal indomethacin and diclofenac in average-risk patients was recently challenged based on the findings of some clinical studies and

meta-analyses.[13–16] Therefore, the aim of this meta-analysis was to provide updated evidence to evaluate the efficacy and safety of rectal indomethacin and diclofenac for prevention of PEP in average-risk patients and to compare the effectiveness of the two agents.

Methods

This study was implemented and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

Literature search and study selection. A comprehensive search was conducted using the PubMed, Embase, and Cochrane Library databases to identify studies published up to May 2021. Subject headings and/or key words used for the search were NSAIDS, nonsteroidal anti-inflammatory drugs, diclofenac, indomethacin, ERCP, endoscopic retrograde cholangiopancreatography, post-ERCP, and pancreatitis, which were combined with boolean operators (AND, OR).[18] The reference lists of retrieved studies were further reviewed to find additional relevant studies. The search was restricted to human studies regardless of language.

Abstracts and articles were included if they met the following criteria: (i) RCTs evaluating the efficacy of rectal indomethacin or diclofenac in preventing PEP, including adult patients only; (ii) the dose of indomethacin or diclofenac was 100 mg; (iii) the control intervention was placebo or no treatment; and (iv) a clear definition of PEP was indicated according to the consensus criteria. The exclusion criteria were as follows: (i) studies comparing the effect of rectal NSAIDs combined with other interventions; (ii) studies including only high-risk patients; and (iii) insufficient data for assessing PEP. The search and inclusion of studies were performed by two reviewers independently. In the case of uncertainty or disagreement, a third reviewer was consulted until all reviewers ultimately reached an agreement by discussion.

Data extraction and risk of bias assessment. Two independent investigators conducted data extraction using a standardized data collection form. The following variables were extracted: author, publication year, country in which the study was performed, study design, intervention and control approaches (type of drug, dose, and timing), sample size, adverse events, and definition and incidence of PEP.

The quality of the included studies was evaluated by two investigators independently with the Cochrane Collaboration tool.[19] The assessment criteria included: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. Discrepancies were resolved by consulting a third investigator and through discussion.

Statistical analysis. For direct comparisons between the treatment and control groups, both fixed- and random-effects models weighted by the Mantel–Haenszel method were employed, and pooled estimates of the relative risk (RR) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. The I^2 statistic was used to evaluate the degree of heterogeneity, with an I^2 value >50% suggesting significant heterogeneity. The adjusted indirect treatment comparison method was used to indirectly compare the effectiveness of indomethacin and diclofenac using the STATA version 14.0 software (Stata Corp, College Station, TX, USA). The Begg adjusted rank correlation test[20] and Egger's regression method[21] were used to evaluate publication bias, which were also conducted in STATA version 14. Other statistical analyses were implemented using Review

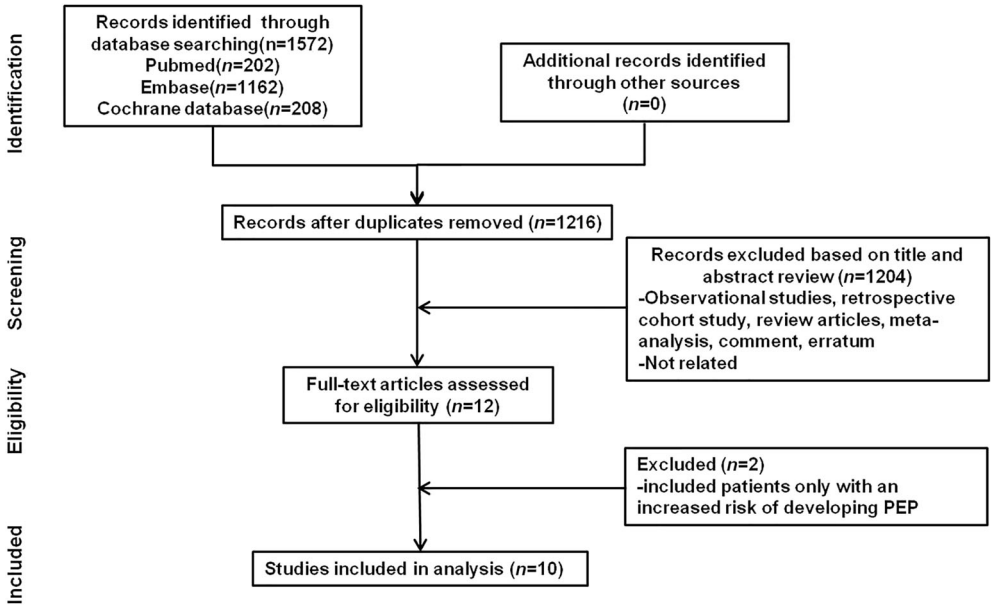

Figure 1 Flowchart of the selection of studies for inclusion in the meta-analysis.

Manager (version 5.3, Cochrane Collaboration, Oxford, UK). $P < 0.05$ was considered to represent statistical significance.

Results

Study selection. The strategy for the literature search is depicted as a flowchart in Figure 1. A total of 1572 potentially relevant publications were identified through the initial search strategy. After discarding 356 duplicates, 1216 records were screened based on the title and abstract, and 1204 publications were excluded. Twelve studies were retained for assessing eligibility, two of which[22,23] were excluded as they only included patients with high risk of developing PEP. Finally, 10 studies[24–33] were included in this meta-analysis.

Characteristics of included studies. The characteristics of the included RCTs are summarized in Table 1. A total of 2928 patients were included in the 10 studies, with 1491 in the treatment group (1366 and 125 patients received indomethacin and diclofenac, respectively) and 1437 in the control group (received placebo or no treatment). All trials were published between 2007 and 2016, including nine full-text articles and one abstract. There was only one multicenter trial. In most studies (7 of 10), the definition of PEP was based on an elevation of serum amylase or lipase levels at least three times above the upper limit of the normal range measured at 24 h following ERCP with new onset or worsening of abdominal pain. In one trial, the serum amylase was measured earlier (2 h after ERCP)[24]; in one trial, it was measured at 2, 12, and 24 h after ERCP[29]; and in one trial, the serum amylase level was required to be greater than four times the upper limit of normal to define PEP.[31] The risk of biased assessments for the included studies is presented in Figure 2.

Analysis of outcomes. In 10 trials, which including average-risk patients for PEP, the incidence of PEP was compared between patients who received rectal-administered NSAIDs and those who received placebo or no treatment. As shown in Figure 3, the pooled estimates using the random-effects model demonstrated a significant association of rectal NSAIDs administration with reduction in the overall risk of PEP compared with the control (RR = 0.62; 95%CI: 0.46–0.83;

Table 1 Characteristics of the included studies

Author, year, country	Type of study	Timing	Intervention	Control	Definition of PEP
Sotoudehmanesh *et al.*, 2007, Iran	Double-blind randomized trial	Immediately before ERCP	Indomethacin	Inert placebo	Amylase >3× ULN, 24 h post-ERCP, with epigastric pain, back pain, and epigastric tenderness
Montaño Loza *et al.*, 2007, Mexico	Randomized clinical trial	2 h before ERCP	Indomethacin	Glycerin suppository	Amylase >3× ULN, 2 h post-ERCP, sharp pain irradiating to the back, and nausea or vomiting
Döbrönte *et al.*, 2012, Hungary	Prospective randomized placebo-controlled trial	10 min before ERCP	Indomethacin	Inert placebo	Amylase, lipase >3× ULN, 24 h post-ERCP, new pancreatic-type pain, and prolonged hospitalization
Döbrönte *et al.*, 2014, Hungary	Multicenter prospective randomized placebo-controlled trial	10–15 min before ERCP	Indomethacin	Inert placebo	Amylase, lipase ≥3× ULN, 24 h post-ERCP, new typical upper abdominal pain requiring prolonged hospitalization
A'rpa'd Patai *et al.*, 2015, Hungary	Prospective double-blind placebo-controlled trial	Within 1 h before ERCP	Indomethacin	placebo	amylase ≥3× ULN, 24 h post-ERCP, pancreatitis-type pain, and extension of hospitalization ≥2 nights
Levenick *et al.*, 2016, USA	Prospective double-blind placebo-controlled trial	During the ERCP	Indomethacin	Inert placebo	New onset upper abdominal pain, increased lipase level > 3 × ULN, 24 h after onset of pain, hospitalization for at least 2 nights
Hosseini *et al.*, 2016, Iran	Randomized clinical trial	2 h before ERCP	Indomethacin	Glycerine suppository	Serum amylase levels ≥3 × ULN, and the patient presented with abdominal pain, nausea, and vomiting
Shafique *et al.*, 2016, Pakistan	Randomized, double blinded, placebo controlled study	before ERCP	Diclofenac	Glycerine suppository	Epigastric pain with guarding and/or vomiting, an elevated pancreatic enzyme (serum amylase) level greater than four-fold the ULN (>400 IU/L)
UÇAR *et al.*, 2016, Turkey	Prospective, randomized controlled study	30–90 min before ERCP	Diclofenac	No treatment	Amylase >3× ULN, and new-onset or worsened abdominal pain lasting more than 24 h post-ERCP
Arain *et al.*, 2013, India	Randomized controlled clinical trial	60 min before ERCP	Diclofenac	No treatment	Amylase ≥3× ULN within 24 h post-ERCP, new upper abdominal pain and hospitalization for at least two nights

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; ULN, upper limit of normal.

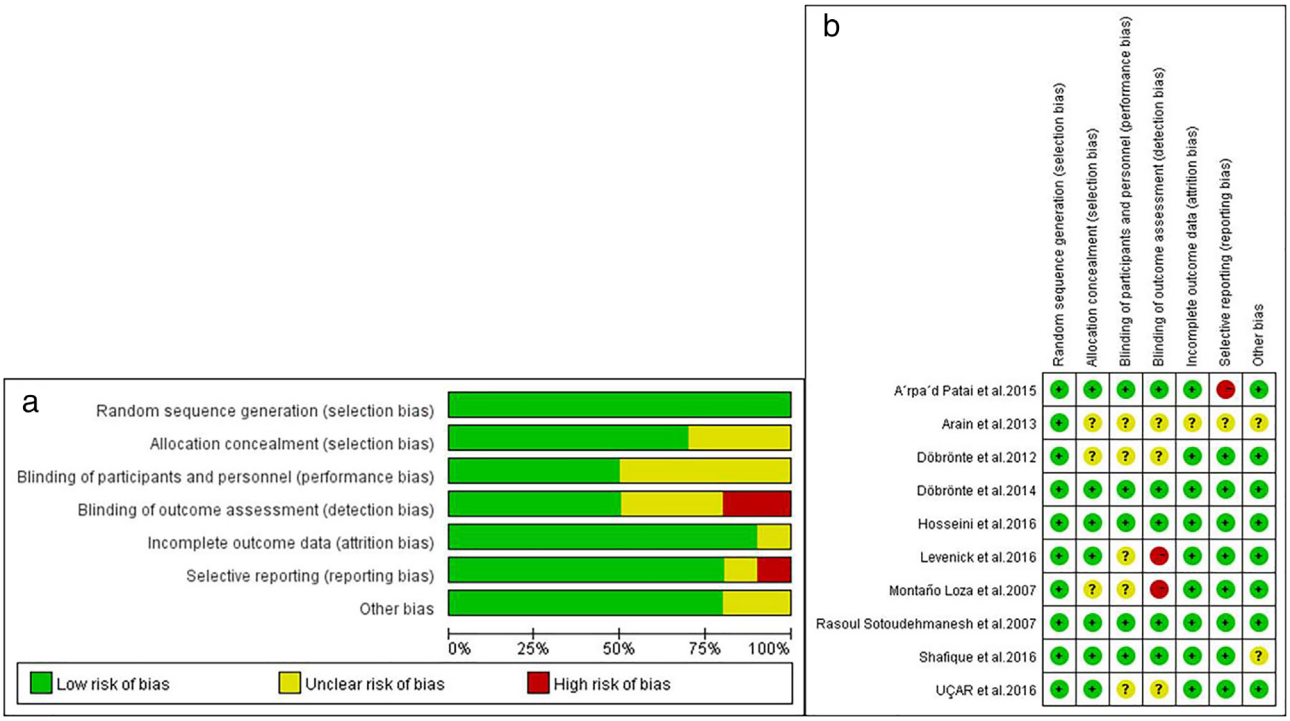

Figure 2 (a) Risk of bias graph. (b) Risk of bias summary. Green: Low risk; yellow: Unclear; red: High risk.

$P = 0.001$), with insignificant heterogeneity ($I^2 = 28\%$). Similar results were also obtained from the fixed-effects model (see Fig. S1, Supporting information). Visual inspection of the funnel plot (Fig. 4) did not provide any evidence of publication bias. Furthermore, both Begg's tests ($P = 0.474$) and Egger's tests ($P = 0.420$) indicated no significant publication bias.

Among the 10 studies, indomethacin was used in 7 and diclofenac was used in 3. The pooled RR for PEP with indomethacin was 0.67 (95% CI: 0.49–0.94; $P = 0.02$) with insignificant heterogeneity ($I^2 = 30\%$), and the pooled RR for PEP with diclofenac was 0.42 (95% CI: 0.23–0.75; $P = 0.003$) with no statistical heterogeneity ($I^2 = 0\%$) (Fig. 5). This comparison indicated that both rectal indomethacin and diclofenac are effective for the prevention of PEP. Similar results were also obtained from the fixed-effects model (see Fig. S2).

To investigate potential differences between indomethacin and diclofenac in preventing PEP, we also implemented indirect comparisons, and found no significant benefits of indomethacin over diclofenac (RR = 1.607; 95% CI: 0.824–3.136).

Adverse events. Among all included reports, only the meeting abstract did not mention the incidence of adverse events. Adverse events were reported in two studies.[28,30] Bleeding was the most commonly recorded adverse event, with 22 cases of bleeding reported in two studies, including 13 (2.6%) in the NSAIDs group and 9 (1.8%) in the control group. Four cases of

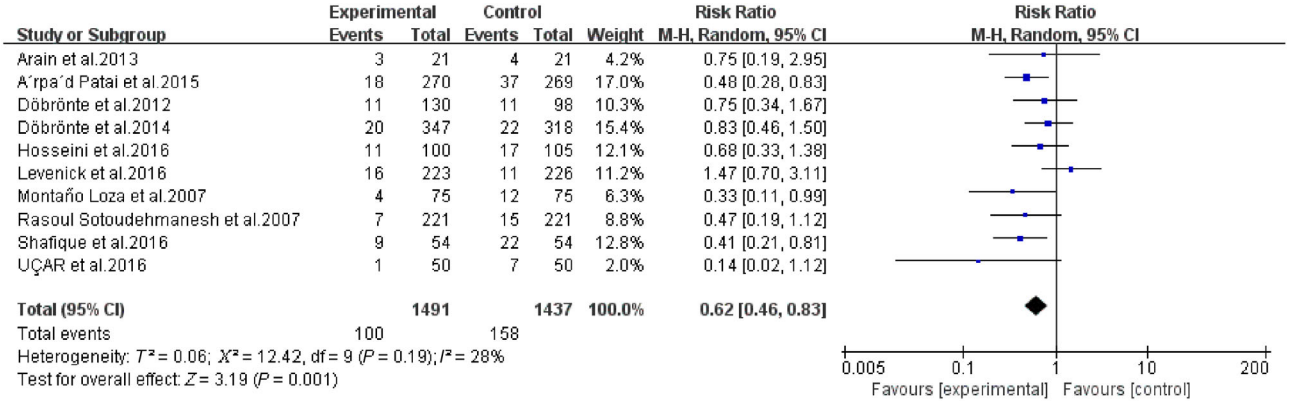

Figure 3 Efficacy of rectal indomethacin and diclofenac in the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis.

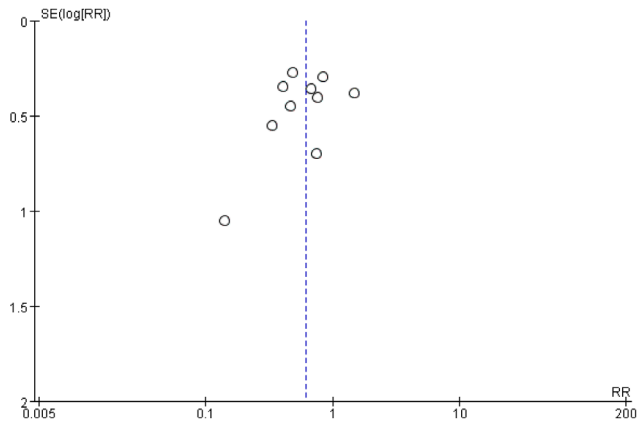

Figure 4 Funnel plot of all included studies to assess publication bias.

post-ERCP cholangitis were reported in one study,[28] including 2 (0.7%) in the NSAIDs group and 2 (0.7%) in the control group. One case of perforation was reported in one study,[28] which occurred in the NSAIDs group. In general, adverse events associated with rectal NSAIDs therapy were rare.

Discussion

There are several underlying mechanisms for pancreatic injury during ERCP, including mechanical, thermal, chemical, hydrostatic, enzymatic, and microbiologic insults.[34] The influence of these factors leads to a cascade of events resulting in the premature intracellular activation of pancreatic proteolytic enzymes, autodigestion, and the release of inflammatory cytokines that produce both local and systemic effects.[3] Phospholipase A2 (PLA2) plays an important role in the initial inflammatory cascade of acute pancreatitis by regulating some proinflammatory mediators.[35,36] Accordingly, NSAIDs, as potent inhibitors of PLA2, have proven to be effective in the prevention of PEP when administrated rectally in several previous RCTs and meta-analyses.

However, two recent meta-analyses indicated that rectal indomethacin was ineffective in preventing PEP in average-risk patients.[13,14] These two meta-analyses analyzed the same six RCTs, and both used the random-effects model for assessing the overall effect of rectal indomethacin on PEP. Interestingly, another meta-analysis[37] that included the same six RCTs but used the fixed-effects model arrived at the opposite conclusion. In fact, the application of fixed-effects model is based on the assumption that studies being analyzed share the same common true effect size. Moreover, if the fixed-effects model is applied to heterogeneous study domains, it would result in inflated Type I error rates and confidence intervals that are substantially narrower than the actual confidence intervals, a substantial inaccuracy, and a substantial overstatement of the precision of the meta-analysis results.[38] As in many cases, the assumption of the same true effect across studies is implausible; random-effects meta-analysis, which accounts for unexplained heterogeneity, may be preferred to the fixed-effects model.[39] In our subgroup analysis, one more RCT[29] was added for the indomethacin group, and both the fixed- and random-effects models were employed. Both analyses demonstrated that rectal indomethacin was actually effective for preventing PEP in average-risk patients.

The effect of rectal diclofenac in the prevention of PEP has also been controversial. A mixed cohort study indicated that

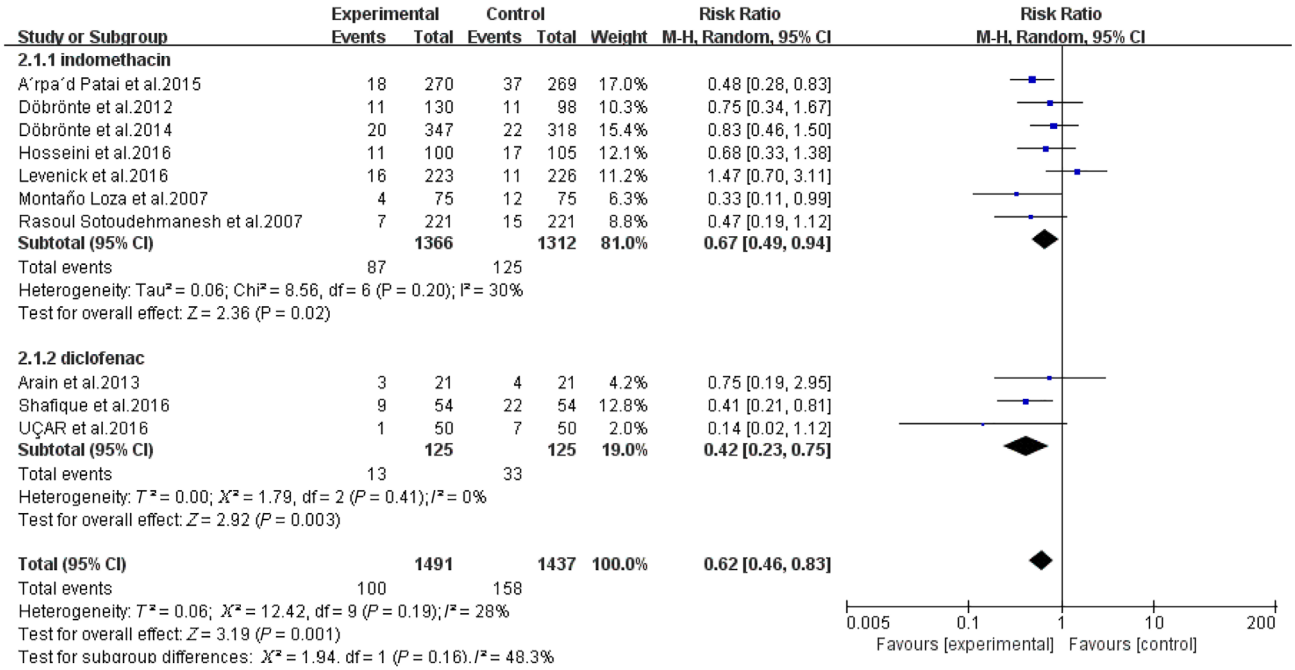

Figure 5 Subgroup analysis according to drug type.

rectal diclofenac administration did not prevent the development of PEP in nonselected consecutive patients following ERCP.[15] Most previous meta-analyses evaluating the efficacy of rectal diclofenac for PEP prophylaxis included both high-risk and average-risk patients. One meta-analysis by Shen *et al*.[37] supported the benefits of rectal diclofenac among unselected patients for PEP prophylaxis. Three RCTs were included in their analysis, but the dose of diclofenac was 25 or 50 mg in one RCT; such a low dose is not commonly used in RCTs assessing rectal NSAIDs for PEP prophylaxis, and has not yet been recommended by any guideline. In our meta-analysis, we excluded the RCT using low-dose diclofenac, and added another recent RCT performed by Shafique *et al*.[31] Similar to the effects observed for indomethacin, our findings demonstrated that rectal diclofenac had a protective effect in average-risk patients in both the fixed- and random-effects models.

Makela *et al*. reported that indomethacin was more potent than diclofenac in inhibiting PLA2 activity in the serum from patients with acute pancreatitis.[40] In addition, diclofenac undergoes first-pass metabolism with only 50–60% of the drug reaching the systemic circulation in an intact form, but indomethacin is not subject to substantial first-pass metabolism.[41] Based on these findings, it is reasonable to speculate that indomethacin may be a better choice than diclofenac in the prevention of PEP. To date, only one clinical trial[42] has directly compared the efficiency of rectal indomethacin and diclofenac in the prevention of PEP among unselected patients. However, in that study, PEP was defined as a more than 300% increase in amylase and lipase levels compared with the baseline value, with a less than threefold increase in the upper normal limit levels, 24 h after the procedure, accompanied by abdominal pain, leading to prolonged hospitalization.[42] This definition is not in conformance with the consensus criteria of acute pancreatitis and differs from the standard definition used in the RCTs included in our meta-analysis. A network meta-analysis of RCTs has been conducted to compare allopurinol, diclofenac, gabexate, glyceryl trinitrate, indomethacin, nafamostat, octreotide, somatostatin, and ulinastatin for protection against PEP. The results showed that diclofenac, gabexate, glyceryl trinitrate, indomethacin, somatostatin, and ulinastatin were more effective than placebo, and no significant differences were found in the efficacy among these drugs.[43] However, in that analysis, administration routes of diclofenac included intramuscular injection and intravenous injection except for rectal administration. In our analysis, we adopted stricter inclusion criteria, including only average-risk patients and rectal administration. Our findings revealed that rectal indomethacin and diclofenac rendered the same effectiveness for PEP prophylaxis in average-risk patients. Further high-quality head-to-head RCTs are needed to validate these findings.

The efficacy and toxicities of NSAIDs are both dose-dependent,[44–46] and the optimal dose of NSAIDs against PEP is unknown yet. Recently, a randomized, double-blind, comparative effectiveness trial showed that dose escalation to rectal indomethacin 200 mg was not more efficacious than the standard 100 mg regimen in reducing pancreatitis after ERCP in high-risk patients, and there was no significant difference in the severity of PEP between the two groups.[41] Another randomized trial showed no benefit of double-dose rectal indomethacin 200 mg compared with the standard single dose,[47] but in this study, the investigated patients were at average risk for PEP, and the time of drug administration was different. The efficacy of low-dose rectal diclofenac for PEP is controversial. A prospective randomized controlled study showed that low-dose (50 mg) rectal diclofenac can prevent PEP in Japanese subjects.[48] Another prospective randomized controlled trial also from Japan, which included more patients, indicated that rectal diclofenac 50 mg did not prevent the occurrence of PEP in patients classified as low or high risk.[49]

The peak concentration of diclofenac and indomethacin in suppository form occurs between 30 and 90 min after insertion[22,25]; thus, pre-ERCP rectal drug administration might achieve better efficacy in preventing PEP. A recent RCT conducted by Luo *et al*.[50] showed that the strategy of prophylactic pre-ERCP administration of rectal indomethacin in all patients was superior to that of selected rectal indomethacin given after ERCP in only high-risk patients to reduce the risk of post-ERCP pancreatitis. Among the RCTs included in our study, the drug (indomethacin) was administered during ERCP in only one,[30] and in the other nine trials, the pre-ERCP administration strategy was chosen. We were unable to perform a subgroup analysis to investigate whether pre-ERCP rectal administration of NSAIDs had a superior effect to those administered post-ERCP. Further trials are warranted to determine the optimal dosage of rectal NSAIDs and optimal timing of administration for preventing PEP.

There are some limitations to our study. First, the limited number of RCTs and patients available for analysis may have caused bias. Second, the heterogeneity of patients and techniques may have influenced the results, such as the race, cannulation technique, and type of precut. Third, differences in some other interventions among studies, such as pancreatic duct stent placement, may have confounded the results.

Conclusion

In conclusion, we suggest that rectal indomethacin and diclofenac are equally efficacious and safe for PEP prophylaxis in average-risk patients, which provides valid evidence for clinical practice. However, there is still much to explore, for instance, whether the combination of rectal NSAIDs and other drugs is superior to rectal NSAIDs alone in preventing PEP, and whether the efficacy of rectal NSAIDs in preventing PEP is different in some special disease states.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Efficacy of rectal indomethacin and diclofenac in PEP prophylaxis using the fixed-effects model.

Figure S2. Subgroup analysis according to drug type using the fixed-effects model.