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ORIGINAL ARTICLE

Nonsteroidal Anti-inflammatory Drugs for Endoscopic Retrograde Cholangiopancreatography Postoperative Pancreatitis Prevention: a Systematic Review and Meta-analysis

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Abstract

Background or Purpose There is controversy regarding the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for prophylaxis against endoscopic retrograde cholangiopancreatography (ERCP) postoperative pancreatitis. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy of NSAIDs for prophylaxis against post-ERCP pancreatitis (PEP).

Methods PubMed, EMBASE, and Cochrane library databases were searched for relevant randomized controlled trials (RCTs). Selected RCTs were pooled under a fixed effects model to generate the relative risks (RRs) and their corresponding 95% confidence intervals (CIs).

Results Nineteen RCTs involving a total of 5031 patients (2555 in the intervention group and 2476 in the control group) were selected. Overall, NSAIDs were associated with a significant reduction in risk of PEP (RR = 0.54, 95% CI 0.45 to 0.64, I^2 = 40.4%) and moderate to severe PEP (RR = 0.45, 95% CI 0.30 to 0.67, I^2 = 0%) compared with the control group. Subgroup analyses were performed according to route of administration (rectal or other), type of NSAIDs (diclofenac, indomethacin, or other), timing of administration (pre-ERCP, post-ERCP, or other), and patient population (high risk or general). Subgroup analyses showed difference in clinical efficacy of NSAID prophylaxis regardless of route, timing, or specific type of NSAID.

Conclusion NSAIDs were associated with a significant reduction in risk of PEP and moderate to severe PEP compared to the control group.

Keywords Nonsteroidal anti-inflammatory drugs · Endoscopic retrograde cholangiopancreatography · Pancreatitis · Randomized controlled trials · Systematic review · Meta-analysis

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a common diagnostic and therapeutic procedure for disorders of the biliary tree and pancreas. Acute pancreatitis is the most frequent and severe complication of ERCP. The occurrence of post-ERCP pancreatitis (PEP) varies between 1 and 25% depending on the risk factors and the indication of ERCP.[1–4] The vast majority of PEP has a mild or moderate course, but in 0.3–0.6% of cases, PEP is severe in nature with a need for intensive care and invasive interventions and, at worst, can even lead to death.[5,6]

Several approaches to reduce the risk of PEP have been investigated. Insertion of pancreatic duct (PD) stents has been shown to reduce the risk of PEP in high-risk patients and the risk of severe PEP.[7–9] However, stent placement has drawbacks, which include failed placement, migration, and ductal perforation.[10,11] Thus, the use of PD stents is limited to patients with an increased risk of moderate to severe pancreatitis. Additionally, a significant proportion of endoscopists decide not to place PD stents due to lack of experience.[12]

Lan Liu and Chenghao Li contributed equally to this work.

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Pharmacological prophylaxis of pancreatitis after PEP has remained favorable in various trials in recent years. Nonsteroidal anti-inflammatory drugs (NSAIDs) have shown the most encouraging results in this respect by attenuating the inflammatory response seen in pancreatitis.[13] NSAIDs like diclofenac inhibit phospholipase A2[14] and suppress neutrophil/endothelial cell attachment, thereby restricting the accumulation of neutrophils at the site of tissue injury. In addition, they inhibit the expression of nitric oxide synthase, which is linked to inflammation and cell damage.[15] Furthermore, NSAIDs are easily administered, inexpensive, and relatively safe when given as a single dose, making them an attractive treatment option.

Thus far, a number of randomized controlled trials (RCTs)[13,14,16–32] have been conducted to investigate the efficacy of NSAIDs for prophylaxis against PEP. However, the results of these trials were conflicting, as several trials[13,14,16,18,19,21,22,24,26–28,30–32] showed promising results, whereas others[17,20,23,25,29] showed null results. Therefore, we performed a systematic review and meta-analysis of published studies to provide a comprehensive assessment of the efficacy of NSAIDs for prophylaxis against PEP.

Materials and Methods

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[33]

Search Strategy

We searched PubMed, Embase, and the Cochrane Library databases for relevant publications up to December 2017. The following search terms and their combinations were used to identify relevant publications: (endoscopic

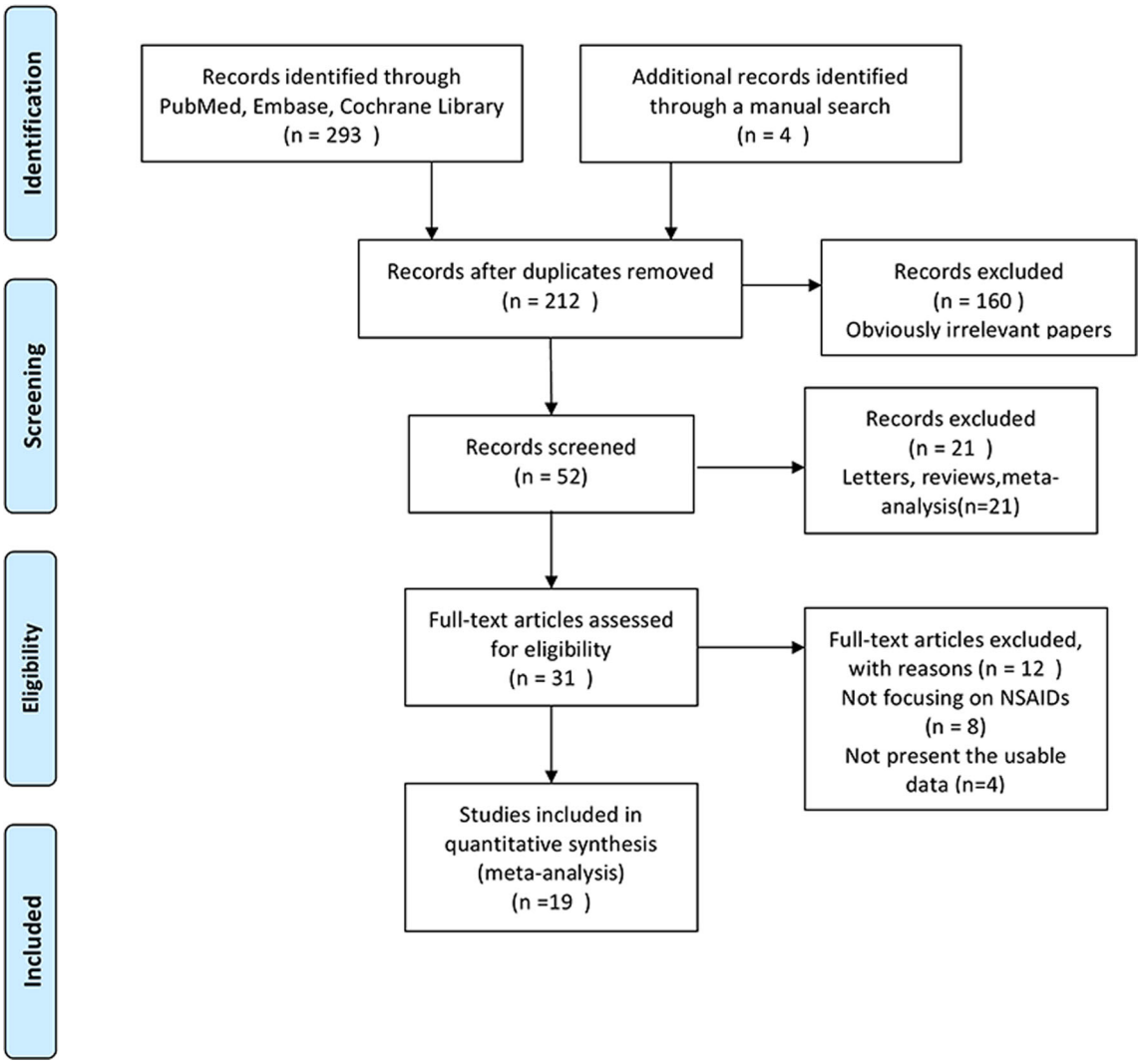

Fig. 1 Flow diagram for studies' identification and selection

Table 1 Characteristics of the studies included in the meta-analysis

Authors/year of publication	Country	Female (%)	Mean age	Study design	Group		Outcomes assessed
					Intervention	Control	
Murray/2003[10]	Scotland	Intervention 62.7; control 67.3	Intervention 55 ± 15 years; control 58 ± 14 years	A single-center, randomized, double-blind, controlled trial	Diclofenac, $N = 110$	Placebo, $N = 110$	Post-ERCP pancreatitis
Cheon/2007[11]	USA	Intervention 78.7; control 75.6	Intervention 45.6 years; control 46 years	A single-center, randomized, double-blind, controlled trial	Diclofenac, $N = 105$	Placebo, $N = 102$	Post-ERCP pancreatitis
Montano Loza/2007	Mexico	Intervention 65.3; control 68	Intervention 55.37 ± 18 years; control 51.12 ± 17 years	A single-center, randomized, single-blind, controlled trial	Indomethacin, $N = 75$	Placebo, $N = 75$	Post-ERCP pancreatitis
Sotoudehmanesh/2007	Iran	Intervention 54.7; control 53.1	Intervention 58.4 ± 17.1 years; control 58.1 ± 16.8 years	A single-center, randomized, double-blind, controlled trial	Indomethacin, $N = 245$	Placebo, $N = 245$	Post-ERCP pancreatitis
Khoshbaten/2008	Iran	Intervention 56; control 50	Intervention 57 ± 15 years; control 60 ± 17 years	A single-center, randomized, double-blind, controlled trial	Diclofenac, $N = 50$	Placebo, $N = 50$	Post-ERCP pancreatitis
Senol/2009	Turkey	Intervention 37.5; control 55	Intervention 60.3 ± 16.1 years; control 59.3 ± 14.5 years	A single-center, randomized controlled trial	Diclofenac, $N = 40$	Placebo, $N = 40$	Post-ERCP pancreatitis
Dobronte/2012	Hungary	Intervention 63; control 70.4	Intervention 66 ± 18 years; control 67 ± 17 years	A single-center, randomized controlled trial	Indomethacin, $N = 130$	Placebo, $N = 98$	Post-ERCP pancreatitis
Elmunzer/2012	USA	Intervention 77.6; control 80.5	Intervention 44.4 ± 13.5 years; control 46 ± 13.1 years	A multicenter, randomized, double-blind, controlled trial	Indomethacin, $N = 295$	Placebo, $N = 307$	Post-ERCP pancreatitis
Otsuka/2012	Japan	Intervention 60.8; control 37.7	Intervention 75 years; control 72 years	A multicenter, randomized, controlled trial	Diclofenac, $N = 51$	Placebo, $N = 53$	Post-ERCP pancreatitis
Dobronte/2014	Hungary	Intervention 61.7; control 66.7	Intervention 65.66 ± 16.21 years; control 67.68 ± 15.56 years	A multicenter, randomized, controlled trial	Indomethacin, $N = 347$	Placebo, $N = 318$	Post-ERCP pancreatitis
Andrade-Davila/2015	Mexico	Intervention 62.19; control 70.23	Intervention 51.59 ± 18.55 years; control 54 ± 17.85 years	A single-center, randomized, controlled trial	Indomethacin, $N = 82$	Placebo, $N = 84$	Post-ERCP pancreatitis
Lua/2015	Malaysia	Intervention 50.7; control 66.7	Intervention 50.3 ± 17.6 years; control 49.6 ± 16.8 years	A single-center, randomized, controlled trial	Diclofenac, $N = 69$	No intervention, $N = 75$	Post-ERCP pancreatitis
Patai/2015	Hungary	Intervention 67; control 67.3	Intervention 66.25 years; control 64.51 years	A single-center, randomized, controlled trial	Indomethacin, $N = 270$	Placebo, $N = 269$	Post-ERCP pancreatitis
Fujita/2016	Japan	Intervention 25.5; control 30.2	Intervention 65.2 years; control 68.1 years	A single-center, randomized, controlled trial	Flurbiprofen, $N = 47$	Placebo, $N = 53$	Post-ERCP pancreatitis
Hosseini/2016	Iran	Intervention 60; control 53.3	Intervention 51.2 ± 12.12 years; control 49 ± 14.26 years	A single-center, randomized, controlled trial	Indomethacin, $N = 100$	Placebo, $N = 105$	Post-ERCP pancreatitis
Levenick/2016	USA	Intervention 52.9; control 52.2	Intervention 64.9 years; control 64.3 years	A single-center, randomized, controlled trial	Indomethacin, $N = 223$	Placebo, $N = 226$	Post-ERCP pancreatitis
Mansour-Ghanaei/2016	Iran	Intervention 48.1; control 45.1	Intervention 46.3 ± 8.3 years; control 44.7 ± 9.7 years	A single-center, randomized, double-blind, controlled trial	Naproxen, $N = 162$	Placebo, $N = 162$	Post-ERCP pancreatitis
Shafque/2016	Pakistan	Intervention 75.92; control 64.81	Intervention 46.09 ± 12.31 years; control 42.93 ± 14.69 years	A single-center, randomized, double-blind, controlled trial	Diclofenac, $N = 54$	Placebo, $N = 54$	Post-ERCP pancreatitis
UCAR/2016	Turkey	Intervention 74; control 60	Intervention 59 ± 18.6 years; control 60.5 ± 17.6 years	A single-center, randomized, controlled trial	Diclofenac, $N = 100$	Placebo, $N = 50$	Post-ERCP pancreatitis

ERCP endoscopic retrograde cholangiopancreatography

retrograde cholangiopancreatography ORERCP) AND pancreatitis AND (nonsteroidal anti-inflammatory drugs ORNSAIDs). We did not impose any language restrictions on database searches. In addition, the references cited in the retrieved manuscripts were also manually searched to identify additional relevant publications that were missed during the database searches.

Selection Criteria

Randomized controlled trials evaluating the efficacy of NSAIDs for prophylaxis against PEP were selected, if they met the following criteria: (1) Reported either the effect estimates, such as RRs with 95% CIs, or sufficient information to calculate these values; (2) reported the following outcomes: the severity of PEP (any, mild, or moderate to severe).

Data Extraction and Quality Assessment

All available data was extracted from each study by two investigators independently based on the inclusion criteria listed above. Any disagreement was resolved through discussion with a third investigator. The following information was extracted from all included studies: first author, year of publication, country, gender, mean age, study design, intervention group, and outcomes assessed. The quality of the RCTs was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias.[34] The assessment included the following components: random sequence generation, allocation concealment, blinding of patients and study personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of outcomes, and other biases to validity.

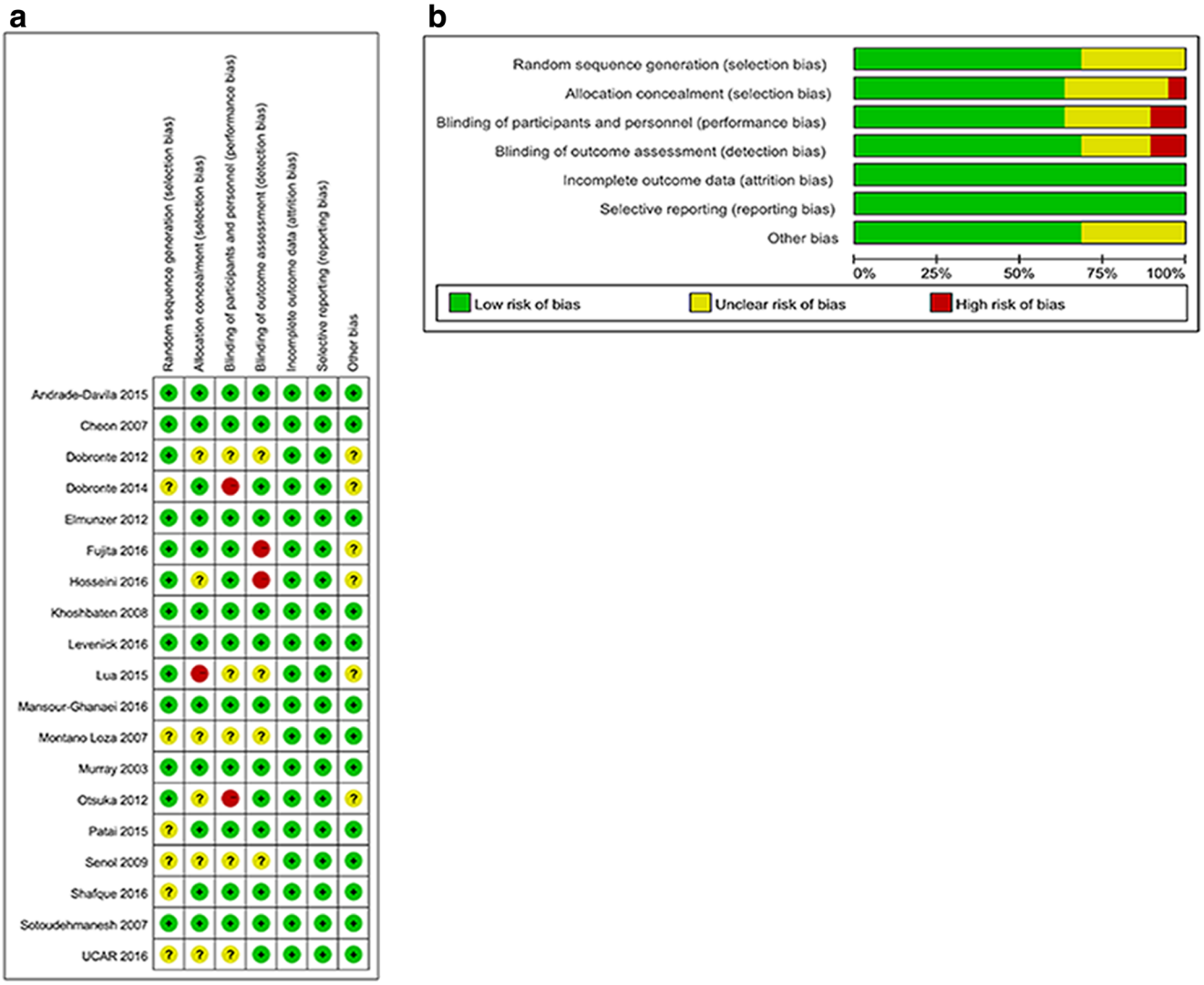

Fig. 2 Risk of bias assessments for the randomized trials included in the meta-analysis. **a** Risk of bias summary. **b** Risk of bias graph. *Symbols*: (+) low risk of bias; (?) unclear risk of bias; (-) high risk of bias

Statistical Analysis

Dichotomous outcomes included rates or proportions from which pooled relative risk (RR) and 95% confidence intervals (CI) were estimated. When $P > 0.1$ or $I^2 < 50\%$, indicating a lack of heterogeneity, for these analyses, the fixed effects model was used; otherwise, the random effects model was applied. Sensitivity analysis by omitting a single study in each turn was performed to assess the relative influence of each study on the pooled estimate. Publication bias was evaluated by visual inspection of symmetry of Begg's funnel plot and assessment of Begg's and Egger's test. Trim and fill analysis was applied if publication bias was detected. The Q and I^2 statistics were used to assess statistical heterogeneity across studies. For the Q statistic, $P < 0.1$ was considered statistically significant; for the I^2 statistic, the following cutoff points were used: < 25% (low heterogeneity), 25–50% (moderate heterogeneity), > 50–75% (high heterogeneity), and > 75% (severe heterogeneity)[35]. One study[32] investigated the prevention of PEP using rectal and intramuscular administration, and the data was analyzed separately for each group; hence, we analyzed them as two separate studies. We performed subgroup analyses according to route of administration (rectal or other), type of NSAIDs (diclofenac, indomethacin, or other), timing of administration (pre-ERCP, post-ERCP, or other), and population (high risk or general). All statistical analyses were performed using STATA Software (version 12.0, StataCorp, College Station, TX). All P values were two-sided, and the level of significance was set at < 0.05.

Results

Study Selection

From the initial electronic database searches, we identified 293 relevant studies. We found four additional studies by searching the reference lists of review articles.[36] Based on the inclusion criteria, 31 articles qualified for full-text evaluation. After evaluation, 12 articles were deemed unsuitable, of which eight were not focused on NSAIDs and four did not present usable data, and hence were excluded. Finally, 19 studies[13,14,16–32] with 5031 patients were included into the present meta-analysis. The flowchart for the selection of studies and reasons for exclusion are presented in Fig. 1.

Characteristics of the Studies

The main characteristics of the selected studies are shown in Table 1. The included studies were published between 2003 and 2016. The studies were performed in various countries, and the study size ranged from 80 to 665 patients (the

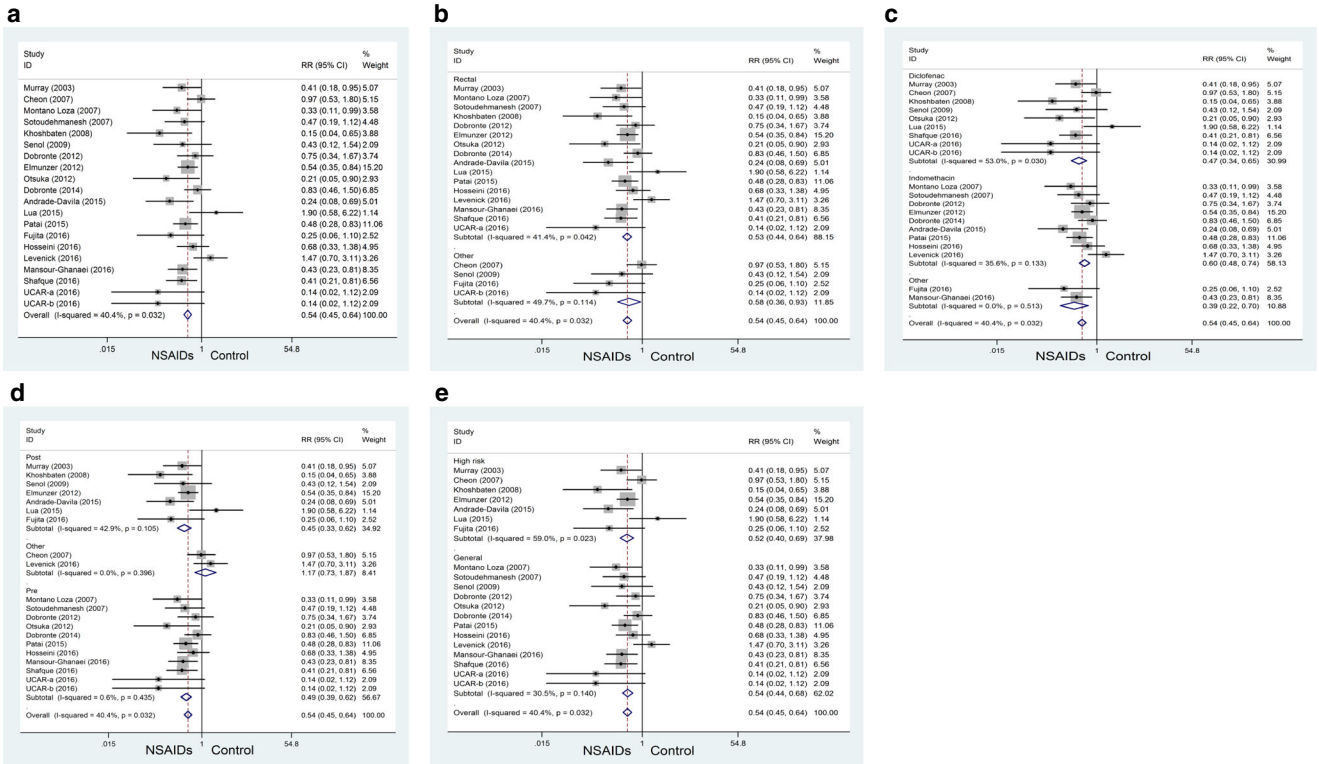

Fig. 3 Effect of NSAIDs for prophylaxis against post-ERCP pancreatitis. **a** Total. **b** Route of administration. **c** Type of NSAIDs. **d** Timing of administration. **e** Patient population

intervention group from 40 to 347 and the control group from 40 to 318). The mean patient age ranged from 42.93 to 75. Nineteen RCTs were included in our meta-analysis, and a total of four different types of NSAIDs were used; diclofenac,[13,14,16,17,22,25,31,32] indomethacin,[18–21,23,24,26,28,29] flurbiprofen,[27] and naproxen.[30] The summary of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases identified for each individual RCT is shown in Fig. 2. All of the included RCTs showed moderate or high quality with acceptable and moderate risk of bias.

Quantitative Synthesis

The Incidence of PEP This outcome was reported in 19 trials that compared NSAIDs to placebo. Of the 5031 patients, 2555 were in the intervention group and 2476 were in the control group. Heterogeneity between these studies was low (I^2 = 40.4%), which was derived from the fixed effects model. Administration of NSAIDs was associated with a significant reduction in risk of PEP compared to the control group (RR = 0.54, 95% CI 0.45 to 0.64, I^2 = 40.4%) (Fig. 3a). All subgroup analyses (Fig. 3b–e) were generally consistent with the overall results and are summarized in Table 2.

The Incidence of Moderate to Severe PEP This outcome was reported in 13 trials[16,17,19,21–27,29,30,32] and compared NSAIDs to placebo. Of the 4071 patients, 2034 were in the intervention group, and 2037 were in the control group. No significant heterogeneity between these studies

Table 2 Subgroup analysis of the meta-analysis

Outcomes	Subgroup	Number of trials	Effect (95% CI)	Estimate for overall effect	Heterogeneity
Any PEP	Total	20	0.54 (0.45, 0.64)	$P < 0.001$	$I^2 = 40.4\%$, $P = 0.032$
	Route of administration				
	Rectal	16	0.53(0.44, 0.64)	$P < 0.001$	$I^2 = 41.4\%$, $P = 0.042$
	Other	4	0.58(0.36, 0.93)	$P = 0.025$	$I^2 = 49.7\%$, $P = 0.114$
	Type of NSAIDs				
	Diclofenac	9	0.47 (0.34, 0.65)	$P < 0.001$	$I^2 = 53\%$, $P = 0.030$
	Indomethacin	9	0.60 (0.48, 0.74)	$P < 0.001$	$I^2 = 35.6\%$, $P = 0.133$
	Other	2	0.39 (0.22, 0.70)	$P = 0.002$	$I^2 = 0\%$, $P = 0.513$
	Timing of administration				
	Pre-ERCP	11	0.49 (0.39, 0.62)	$P < 0.001$	$I^2 = 0.6\%$, $P = 0.435$
	Post-ERCP	7	0.45 (0.33, 0.62)	$P < 0.001$	$I^2 = 42.9\%$, $P = 0.105$
	Other	2	1.17 (0.73, 1.87)	$P = 0.523$	$I^2 = 0\%$, $P = 0.396$
	Population				
	High risk	7	0.52 (0.40, 0.69)	$P < 0.001$	$I^2 = 59\%$, $P = 0.023$
	General	13	0.54 (0.44, 0.68)	$P < 0.001$	$I^2 = 30.5\%$, $P = 0.140$
Severe PEP	Total	14	0.45 (0.30, 0.67)	$P < 0.001$	$I^2 = 0\%$, $P = 0.740$
	Route of administration				
	Rectal	11	0.48(0.32, 0.73)	$P = 0.001$	$I^2 = 0\%$, $P = 0.664$
	Other	3	0.23(0.05, 1.06)	$P = 0.059$	$I^2 = 0\%$, $P = 0.509$
	Type of NSAIDs				
	Diclofenac	6	0.45 (0.19, 1.07)	$P = 0.072$	$I^2 = 14.4\%$, $P = 0.322$
	Indomethacin	6	0.48 (0.29, 0.80)	$P = 0.004$	$I^2 = 0\%$, $P = 0.722$
	Other	2	0.34 (0.12, 0.98)	$P = 0.045$	$I^2 = 0\%$, $P = 0.567$
	Timing of administration				
	Pre-ERCP	7	0.37 (0.20, 0.70)	$P = 0.002$	$I^2 = 0\%$, $P = 0.599$
	Post-ERCP	5	0.53 (0.31, 0.92)	$P = 0.023$	$I^2 = 8.1\%$, $P = 0.361$
	Other	2	0.43 (0.06, 2.89)	$P = 0.382$	$I^2 = 0\%$, $P = 0.449$
	Population				
	High risk	6	0.54 (0.32, 0.93)	$P = 0.025$	$I^2 = 0\%$, $P = 0.472$
	General	8	0.36 (0.20, 0.67)	$P = 0.001$	$I^2 = 0\%$, $P = 0.684$

CI, confidence interval; *ERCP*, endoscopic retrograde cholangiopancreatography; *PEP*, post-ERCP pancreatitis; *NSAIDs*, nonsteroidal anti-inflammatory drugs

was found ($I^2 = 0\%$) using the fixed effects model. Administration of NSAIDs was associated with a significant reduction in the risk of moderate to severe PEP compared to the control group (RR = 0.45, 95% CI 0.30 to 0.67, $I^2 = 0\%$) (Fig. 4a). All subgroup results (Fig. 4b–e) were generally consistent with the overall results and are summarized in Table 2.

Sensitivity Analysis

Sensitivity analysis revealed that the overall results were free from the influence of a single study (Fig. 5).

Publication Bias

Begg's and Egger's regression test demonstrated no evidence of asymmetrical distribution in the funnel plot for the incidence of moderate to severe PEP (Begg's test $P = 0.381$; Egger's test $P = 0.337$) (Fig. 6a). However, Begg's test showed the presence of publication bias for incidence of PEP (Begg's test $P = 0.019$; Egger's test $P = 0.053$) (Fig. 6b). The results remained statistically significant after trim and fill method was performed, suggesting that there were no studies to be filled (Fig. S1).

Discussion

The meta-analysis included 19 RCTs with 5031 patients (2555 in the intervention group and 2476 in the control group) demonstrated that NSAIDs were associated with a significant reduction in risk of post-ERCP pancreatitis and moderate to severe PEP compared to the control group.

The efficacy of NSAIDs for prophylaxis against PEP has been investigated in several previous meta-analyses.[37–39] To our knowledge, the current meta-analysis is the largest and most comprehensive in investigating the efficacy of NSAIDs for prophylaxis against PEP and consisted of 5031 patients from 19 RCTs. Recently, Yang et al[39] conducted a comprehensive meta-analysis on the efficacy of NSAIDs for prophylaxis against PEP. Compared to the meta-analysis conducted by Yang et al., we included seven additional studies.[14,17,25,27,28,31,32] In addition, we performed more comprehensive subgroup analyses compared to the work performed by Hou et al.[37] The study by Luo et al.[38] from a meta-analysis by Hou et al. was not included in our meta-analysis because of the treatment and control group receiving NSAID administration.

Rectal NSAID administration has shown potential benefit on PEP prevention despite conflicting findings in multiple single-center RCTs. Elmunzer et al. performed a multicenter RCT comparing a single dose of 100 mg of rectal

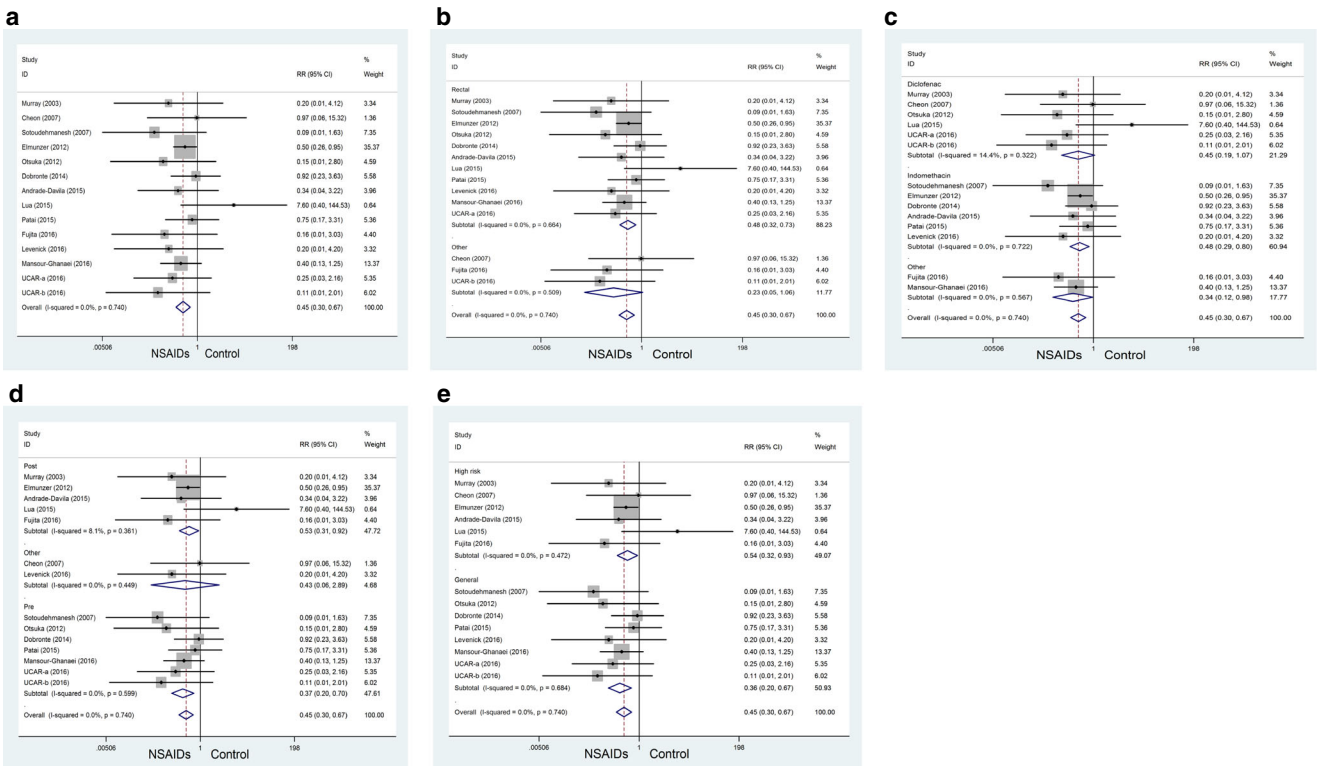

Fig. 4 Effect of NSAIDs for prophylaxis against moderate to severe post-ERCP pancreatitis. **a** Total. **b** Route of administration. **c** Type of NSAIDs. **d** Timing of administration. **e** Patient population

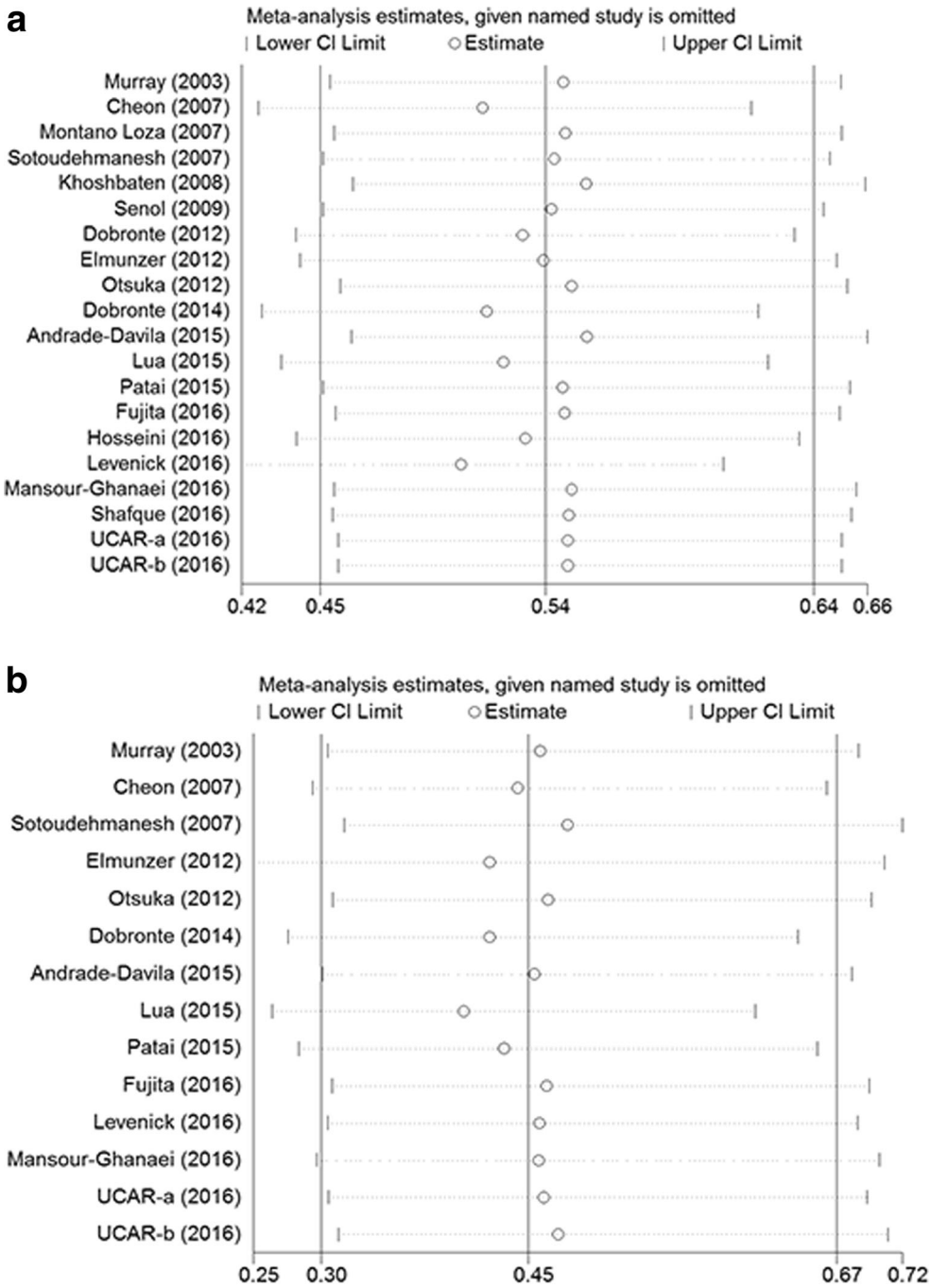

Fig. 5 Sensitivity analysis of the effect of NSAIDs for prophylaxis against post-ERCP pancreatitis. **a** Incidence of post-ERCP pancreatitis. **b** Incidence of moderate to severe post-ERCP pancreatitis

indomethacin to placebo following ERCP in selected high-risk patients and found that 9.2% of patients in the indomethacin group developed PEP compared to 16.9% in the placebo group, demonstrating a statistically significant difference ($P = 0.005$).[21] The incidence of moderate to severe pancreatitis was also significantly decreased in the indomethacin group compared to that in the placebo. However, the majority of patients in this study had possible sphincter of Oddi dysfunction, thus limiting the generalizability of the findings. For such patients, the benefit of ERCP is unclear and there may be an elevated risk of PEP.[40] Additionally, the majority of patients also had a PD stent attempted or placed, and as a result, it was unclear whether indomethacin was the sole contributor for the improved outcomes. Finally, the authors specifically excluded patients with malignant biliary obstruction and patients with other common low-risk indications for ERCP. In a subsequent meta-analysis of 7 RCTs with a total of 2133 patients, rectal indomethacin demonstrated a similar reduction in PEP.[41] However, the majority of patients were at high risk and all studies included patients with suspected SOD.[41] A recent

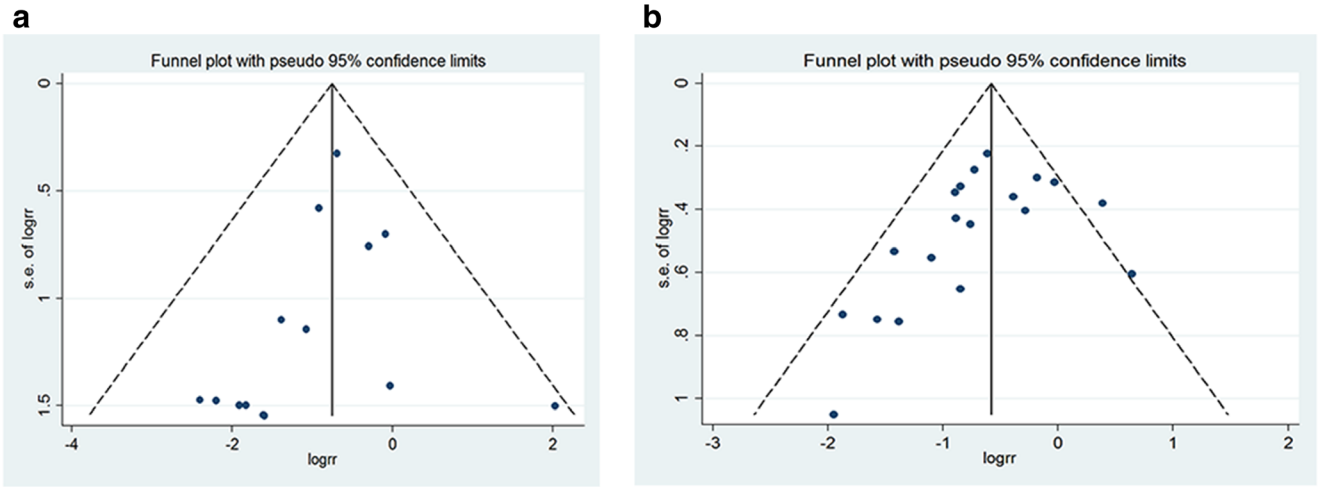

Fig. 6 Funnel plot for publication bias. Each point represents a separate study for the indicated association. **a** Incidence of moderate to severe post-ERCP pancreatitis. **b** Incidence of post-ERCP pancreatitis

RCT involving mainly average-risk patients failed to find a benefit with rectal indomethacin administration when compared to placebo.[29] Therefore, the benefit of rectal NSAIDs has not been definitively demonstrated in low-risk patients and patients with malignant obstruction, who, together, comprise the majority of patients undergoing ERCP in real-world practice.[1]

Several limitations of our meta-analysis should be addressed. Firstly, the characteristics of the included patients, diagnostic criteria of pancreatitis as well as the criteria of pancreatitis severity, definition of the risk stratification of the patients, administration dose, and intervention regimen varied across studies, which may influence the results, hence limiting comparability to some extent. Secondly, there may have been potential publication bias in this meta-analysis since we did not include several unpublished papers because the data was not available to us. Thirdly, our results were based on unadjusted assessment of RRs, which may influence our results. Based on these limitations mentioned above, the results should be regarded with caution.

Conclusion

In conclusion, despite the limitations of our meta-analysis, our study confirmed that NSAIDs were associated with a significant reduction in risk of post-ERCP pancreatitis and moderate to severe PEP compared to the control group, especially via rectal administration. Further studies with larger cohorts and well-designed protocols are required to validate our findings.

Author Contributions Lan Liu and Haiyan Jin conceived and supervised the study; Lan Liu, Chenghao Li, and Yuan Huang performed the research; Lan Liu and Chenghao Li analyzed and interpreted the data; Lan Liu and Haiyan Jin wrote the manuscript; Yuan Huang and Haiyan Jin made manuscript revisions. All authors reviewed the results and approved the final version of the manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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