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# Rectal nonsteroidal anti-inflammatory drugs, glyceryl trinitrate, or combinations for prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: A network meta-analysis

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## Abstract

### BACKGROUND

Acute pancreatitis is the most common and severe complication of endoscopic retrograde cholangiopancreatography (ERCP). Recent evidence suggests that combinations based on rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are more beneficial in preventing post-ERCP pancreatitis (PEP). Randomized controlled trials (RCTs) have also demonstrated the efficacy of glyceryl trinitrate (GTN). We conducted a network meta-analysis to compare NSAIDs and GTN for prevention of PEP and to determine whether they are better in combination.

### AIM

To compare NSAIDs and GTN for prevention of PEP and to determine whether they are better in combination.

### METHODS

A systematic search was done for full-text RCTs of PEP in PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials database. Inclusion and exclusion criteria were used to screen for eligible RCTs. The major data were extracted by two independent reviewers. The frequentist model was used to conduct this network meta-analysis and obtain the pairwise OR and 95%CI. The data were then extracted and assessed on the basis of the *Reference Citation*

Analysis (<https://www.referencecitationanalysis.com/>).

## RESULTS

Twenty-four eligible RCTs were selected, evaluating seven preventive strategies in 9416 patients. Rectal indomethacin 100 mg plus sublingual GTN (OR: 0.21, 95%CI: 0.09–0.50), rectal diclofenac 100 mg (0.34, 0.18–0.65), sublingual GTN (0.34, 0.12–0.97), and rectal indomethacin 100 mg (0.49, 0.33–0.73) were all more efficacious than placebo in preventing PEP. The combination of rectal indomethacin and sublingual GTN had the highest surface under the cumulative ranking curves (SUCRA) probability of (92.2%) and was the best preventive strategy for moderate-to-severe PEP with a SUCRA probability of (89.2%).

## CONCLUSION

Combination of rectal indomethacin 100 mg with sublingual GTN offered better prevention of PEP than when used alone and could alleviate the severity of PEP.

**Key Words:** Endoscopic retrograde cholangiopancreatography; Pancreatitis; Diclofenac; Indomethacin; Naproxen; Glyceryl trinitrate

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**Core tip:** Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a common and serious complication. Several prophylactic measures have been tried. Some guidelines recommend rectal administration of 100 mg diclofenac or indomethacin as routine PEP prophylaxis. glyceryl trinitrate (GTN) has been reported as an effective drug for preventing PEP. In view of some high-quality randomized controlled trials, we conducted this network meta-analysis to compare nonsteroidal anti-inflammatory drugs and GTN for prevention of PEP and to determine whether they are better in combination. Our analysis showed that combination of rectal indomethacin 100 mg with sublingual GTN was the most effective strategy for preventing PEP and reducing its severity.

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## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used tool for diagnosing and treating biliary and pancreatic diseases. Despite technological advances and improved operator experience, ERCP has a high potential for complications, such as acute pancreatitis, bleeding, perforation, and cholangitis[1,2]. Post-ERCP pancreatitis (PEP) is the most common and serious complication, with an incidence of 3.5%–9.7% and mortality ranging from 0.1% to 0.7% [2]. It often leads to prolonged hospitalization and has a substantial economic impact[3].

Over the past few decades, several prophylactic measures have been explored to solve this thorny problem. These include the placement of pancreatic stents, intravenous fluids, and several pharmacological options[4,5]. Some guidelines recommend rectal administration of 100 mg diclofenac or indomethacin as routine PEP prophylaxis in unselected patients. Its efficacy and safety have been confirmed repeatedly[6]. Nevertheless, increasingly, studies have focused on combination therapy involving nonsteroidal anti-inflammatory drugs (NSAIDs) to investigate whether this might be more effective than NSAIDs alone[5,7].

A meta-analysis has confirmed that glyceryl trinitrate (GTN), an inexpensive and easily administered agent, effectively prevents PEP[8]. It has been suggested that a combination of GTN and NSAIDs may be more effective[9]. Therefore, we conducted a network meta-analysis of RCTs to compare the direct and indirect evidence and identify their effectiveness in preventing PEP.

## MATERIALS AND METHODS

### Search strategy

A comprehensive search was conducted independently by two review authors (Shi QQ and Ning XY). The following databases were searched: PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials, from initiation to September 10, 2021. The search terms included “pancreatitis” and “cholangiopancreatography, Endoscopic retrograde” or “Endoscopic retrograde cholangiopancreatography” or “ERCP” and “random or randomized controlled trial” or “RCT”. The terms were limited to “title and abstract” and filtered with “human”. Only articles published in English were selected. The reference lists of related systematic reviews or meta-analyses were manually searched to avoid omitting eligible studies.

### Selection criteria

The inclusion criteria were as follows: (1) RCTs published in full text and English, irrespective of whether double-blind; (2) Patients were subjected to ERCP and administration of rectal NSAIDs, sublingual GTN, or transdermal GTN to prevent PEP; and (3) Incidence of PEP was the primary outcome, and the definition of PEP was explicit. We excluded conference proceedings or abstracts, except where the complete information was available from the authors. We also excluded studies without a record of PEP.

### Data extraction

The following data were extracted by two independent investigators (Shi QQ and Ning XY) from eligible RCTs using a common data form: first author, year of publication, country of origin, patient characteristics (ratio of men to women, age distribution), details of intervention and control, PEP definition, PEP severity criteria, sample size, and the incidence of PEP and its severity. The type, dose, route, and timing of medication were also extracted. Any conflicts were resolved through discussion or consultation with a third reviewer (Yang JR). The data were then extracted and assessed on the basis of the *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>).

### Risk of bias assessment

The Cochrane Risk of Bias Assessment Tool was used by two authors to independently evaluate the risk of bias of individual studies (Li W and Huang GX)[10]. The assessment included the following items: Random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and additional potential practices. Any disagreements were resolved through discussion or consultation with a third reviewer (Yang JR).

### Statistical analysis

This network meta-analysis was undertaken with a Frequentist model using the *mumeta* and *network* commands in STATA version 16.0. The pairwise meta-analysis and network meta-analysis were undertaken simultaneously with the random effect model. The OR and 95%CI were used to describe dichotomous outcomes, and the global and local inconsistencies were checked.  $I^2$  was used to describe the heterogeneity, where  $< 50\%$  indicated low heterogeneity and  $> 50\%$  high heterogeneity.  $P < 0.05$  represented statistical significance. The loop-specific inconsistency was used to assess the discordance between direct and indirect evidence in the loop. If the 95%CI of inconsistency factors included zero or RoR included 1, inconsistency results were considered nonsignificant. The network graph was used to present the treatment comparisons. Interventions were ranked by their posterior probability by the surface under the cumulative ranking curve values.

### Role of funding source

There was no funding source for this study.

## RESULTS

### Eligible studies

The literature search yielded 3260 titles, of which 2905 articles were excluded because they were duplicates, systematic reviews or meta-analyses, or not relevant. Of the remaining 355 articles, 52 were screened out by scanning the titles and abstracts (Figure 1). Eventually, 24 RCTs (including 9416 patients) were included in this network meta-analysis. Sixteen RCTs involved NSAIDs[11-26] and eight were of GTN[9,27-33]. Two different studies had the same first author[12,33], and both of them were included. One study stratified the patients based on pancreatitis risk after ERCP[21]. In the treatment group, the average-risk patients only received 100 mg of rectal indomethacin before ERCP, but the high-risk patients received a further 100 mg of rectal indomethacin after ERCP. Therefore, we only extracted

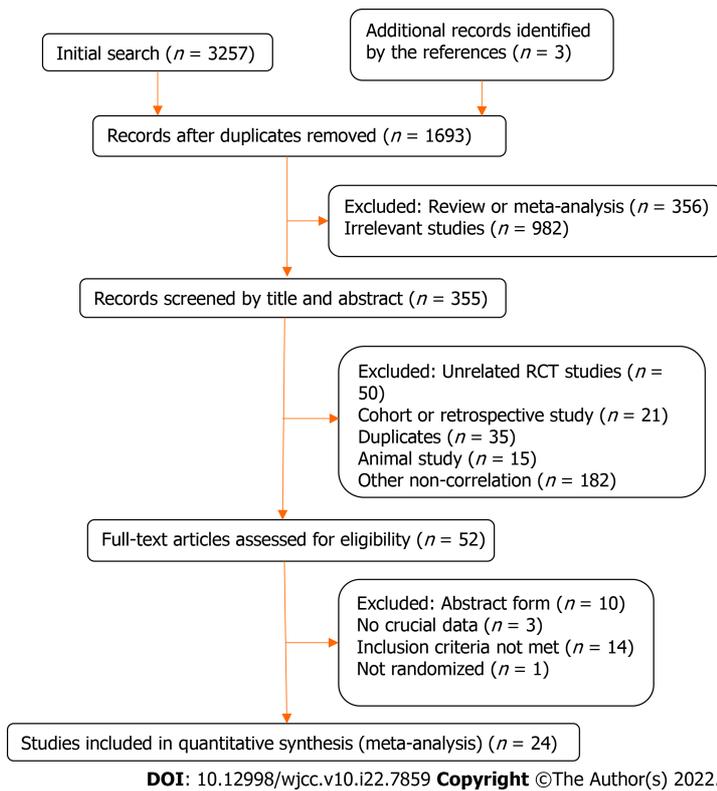


Figure 1 Flowchart of the selection process.

the data of the average-risk patients. One study only included female patients[9], but the baselines between the experimental and control groups were similar, so we included it.

### Characteristics of studies

The main characteristics and the incidence and severity of PEP are presented in Table 1 and Table 2. Among the RCTs that met the inclusion criteria, the first study was published in 2001, and the most recent was in 2020. The sample size ranged from 74 to 2014 subjects. The proportion of women in the RCTs ranged from 37.74% to 100%. A total of 9416 patients were randomly assigned to one of seven different interventions or placebo. The interventions included NSAIDs (100 mg diclofenac, indomethacin, 50 mg diclofenac, naproxen), GTN (sublingual or transdermal), or a combination (indomethacin plus sublingual GTN). The definition and the degree of severity of PEP varied among the included studies, but most of them (66.67%) used the consensus definition[34], with the others using similar definitions. The incidence of PEP was reported in all studies, but four RCTs have no report about the degree of PEP[13,25,27,30].

### Methodological quality and risk of bias

Two authors evaluated the methodological quality of the included RCTs using the Cochrane Collaboration’s Risk of Bias tool. A summary assessment of low, unclear, or high risk of bias was given to each study. The results are presented in Figure 2.

### Consistency test and sensitivity analysis

The inconsistency was not significant ( $I^2 = 3.13\%$ ,  $P = 0.37$ ) among the included RCTs, and no evidence of local or loop inconsistency was seen. A sensitivity analysis was conducted by excluding the studies with the largest ( $n = 2014$ ) and smallest ( $n = 74$ ) sample sizes. This slightly changed the OR and the SUCRA, indicating low heterogeneity ( $I^2 = 2.47\%$ ,  $P = 0.48$ ). The exclusion of two open-label studies[18, 23] also did not change the final results.

### NMA of the PEP incidence

Figure 3A displays the network of all the interventions included in this network meta-analysis, and Figure 3B displays the network of interventions with details of the incidence of mild or moderate-severe PEP recorded. The network meta-analysis included one head-to-head three-arm RCT comparing different NSAIDs, one head-to-head two-arm RCT comparing combined indomethacin and sublingual GTN with indomethacin. All the others were placebo-controlled RCTs.

**Table 1** Characteristics of the included studies

Ref.	Country	Intervention	Sample size
Murray <i>et al</i> [11], 2003	Scotland	100 mg diclofenac after endoscopy	220
Sotoudehmanesh <i>et al</i> [12], 2007	Iran	100 mg indomethacin before ERCP	490
Khoshbaten <i>et al</i> [13], 2007	Iran	100 mg diclofenac after endoscopy	100
Elmunzer <i>et al</i> [14], 2012	United States	100 mg indomethacin after ERCP	602
Otsuka <i>et al</i> [15], 2012	Japan	50 mg diclofenac before ERCP	104
Döbrönte <i>et al</i> [16], 2014	Hungary	100 mg indomethacin 10-15 min before ERCP	665
Andrade-Dávila <i>et al</i> [17], 2015	México	100 mg indomethacin after ERCP	166
Lua <i>et al</i> [18], 2015	Malaysia	100 mg diclofenac after ERCP	144
Patai <i>et al</i> [19], 2015	Hungary	100 mg indomethacin 1 h before ERCP	539
Levenick <i>et al</i> [20], 2016	United States	100 mg indomethacin following attempted cannulation	449
Luo <i>et al</i> [21], 2016	China	100 mg indomethacin within 30 min before ERCP	2014
Mansour-Ghanaei <i>et al</i> [22], 2016	Iran	500 mg naproxen immediately before ERCP	324
Patil <i>et al</i> [23], 2016	India	100 mg diclofenac immediately before or during the ERCP	400
Mohammad <i>et al</i> [24], 2017	Iran	100 mg diclofenac, 100 mg indomethacin or 500 mg naproxen, 30 min before ERCP	246
Li <i>et al</i> [25], 2019	China	100 mg indomethacin before ERCP	100
Katoh <i>et al</i> [26], 2019	Japan	50 mg diclofenac before ERCP	297
Sudhindran <i>et al</i> [27], 2001	United Kingdom	Sublingual 2 mg GTN before ERCP	186
Moretó <i>et al</i> [28], 2003	Spain	Transdermal 15 mg GTN 30 to 40 minutes before ERCP	144
Kaffes <i>et al</i> [29], 2006	Australia	Transdermal 5 mg GTN before ERCP	318
Hao <i>et al</i> [30], 2009	China	Sublingual 5 mg GTN 5 min before ERCP	74
Nøjgaard <i>et al</i> [31], 2009	France	Transdermal 15 mg GTN before ERCP	806
Bhatia <i>et al</i> [32], 2011	India	Transdermal GTN 30 min before ERCP	250
Sotoudehmanesh <i>et al</i> [33], 2014	Iran	100 mg indomethacin, plus 5 mg of sublingual GTN before ERCP	300
Wang <i>et al</i> [9], 2020	China	Indomethacin plus 0.5 mg of sublingual GTN 5 min before ERCP	352

ERCP: Endoscopic retrograde cholangiopancreatography; GTN: Glyceryl trinitrate.

### **Incidence of PEP**

On pairwise comparison with placebo, rectal indomethacin 100 mg plus sublingual GTN (OR: 0.21, 95%CI: 0.09–0.50), rectal diclofenac 100 mg (0.34, 0.18–0.65), sublingual GTN (0.34, 0.12–0.97), and rectal indomethacin 100 mg (0.49, 0.33–0.73) were all more efficacious than placebo in preventing PEP. Rectal indomethacin 50 mg (0.69, 0.22–2.18), transdermal GTN (0.70, 0.37–1.32), rectal naproxen 500 mg (0.80, 0.35–1.83) were found to have no significant effect in preventing PEP (Table 3). Furthermore, the combination of rectal indomethacin 100 mg and sublingual GTN was more effective than rectal naproxen 500 mg (0.26, 0.08–0.86), and transdermal GTN (0.30, 0.10–0.89) in preventing PEP. As shown in Figure 4A, rectal diclofenac 100 mg performed best in the pairwise comparisons of prophylaxis between NSAIDs. Rectal indomethacin 100 mg ranked second. Regarding GTN, sublingual administration was more effective than transdermal in preventing PEP, but the combination achieved the best results.

### **Incidence of mild PEP**

On pairwise comparison with placebo, rectal indomethacin 100 mg plus GTN (0.27, 0.11–0.67), rectal diclofenac 100 mg (0.46, 0.23–0.94), rectal indomethacin 100 mg (0.59, 0.40–0.88) were all more efficacious than placebo in preventing mild PEP (Table 4). The combination of indomethacin with sublingual GTN was also the most effective measure for preventing mild PEP (Figure 4B).

### **Incidence of moderate-severe PEP**

On pairwise comparison with placebo, rectal indomethacin 100 mg plus GTN (0.19, 0.08–0.48), rectal diclofenac 100 mg (0.27, 0.09–0.79), and rectal indomethacin 100 mg (0.43, 0.28–0.66) were all more

**Table 2** Incidence and severity of post- endoscopic retrograde cholangiopancreatography pancreatitis

Ref.	Group	Case (n)	PEP		Sex (M:F)	Age (yr)
			Mild PEP	Moderate to severe PEP		
Murray <i>et al</i> [11], 2003	Diclofenac 100 mg	110	7	0	NA	NA
	Placebo	110	15	2	NA	NA
Sotoudehmanesh <i>et al</i> [12], 2007	Indomethacin	245	7	0	111:134	58.4 ± 17.1
	Placebo	245	10	5	115:130	58.4 ± 16.8
Elmunzer <i>et al</i> [14], 2012	Indomethacin	295	14	13	66:29	44.4 ± 13.5
	Placebo	307	25	27	60:47	46.0 ± 13.1
Otsuka <i>et al</i> [15], 2012	Diclofenac 50 mg	51	2	0	20:31	75
	Placebo	53	7	3	33:20	72
Döbrönte <i>et al</i> [16], 2014	Indomethacin	347	16	4	133:214	65.66 ± 16.21
	Placebo	318	18	4	106:212	67.68 ± 15.56
Andrade-Dávila <i>et al</i> [17], 2015	Indomethacin	82	3	1	31:51	51.59 ± 18.55
	Placebo	84	14	4	25:59	54.0 ± 17.85
Lua <i>et al</i> [18], 2015	Diclofenac 100 mg	69	4	3	34:35	50.3 ± 17.6
	Placebo	75	4	0	25:50	49.6 ± 16.8
Patai <i>et al</i> [19], 2015	Indomethacin	270	15	3	89:181	66.25 (23-100)
	Placebo	269	33	4	88:181	64.51 (20-95)
Levenick <i>et al</i> [20], 2016	Indomethacin	223	16	0	105:118	64.9
	Placebo	226	9	2	108:118	64.3
Luo <i>et al</i> [21], 2016	Indomethacin	992	22	7	NA	NA
	Placebo	1022	48	17	NA	NA
Mansour-Ghanaei <i>et al</i> [22], 2016	Naproxen	162	8	4	84:78	46.3 ± 8.3
	Placebo	162	18	10	89:73	44.7 ± 9.7
Patil <i>et al</i> [23], 2016	Diclofenac 100 mg	200	6	0	72:128	45.44
	Placebo	200	14	9	77:23	47.86
Mohammad <i>et al</i> [24], 2017	Diclofenac 100 mg	124	2	3	58:66	56.5 ± 18.7
	Indomethacin	122	3	4	57:65	58.0 ± 16.8
	Naproxen	126	7	12	60:66	54.8 ± 13.7
Katoh <i>et al</i> [26], 2019	Diclofenac 50 mg	147	7	1	82:65	74.3 ± 11.8
	Placebo	150	4	1	95:55	74.0 ± 12.7
Moretó <i>et al</i> [28], 2003	tra-GTN	71	2	1	44:27	66.7 ± 2
	Placebo	73	10	1	43:30	65.2 ± 2
Kaffes <i>et al</i> [29], 2006	tra-GTN	155	9	2	59:96	60 (47-72)
	Placebo	163	6	4	57:106	65 (54-75)
Nøjgaard <i>et al</i> [31], 2009	tra-GTN	401	4	14	164:237	67(18-95)
	Placebo	405	9	20	168:237	65(19-96)
Bhatia <i>et al</i> [32], 2011	tra-GTN	124	12	0	36:88	42 (18-76)
	Placebo	126	13	0	47:79	42.5 (19-90)
Sotoudehmanesh <i>et al</i> [33], 2014	Indomethacin+sub-GTN	150	8	2	76:74	58.4 ± 17.8
	Placebo	150	19	4	70:80	58.6 ± 17.5
Wang <i>et al</i> [9], 2020	Indomethacin+sub-GTN	176	5	4	Female	63.5 ± 14.4

Placebo	176	14	20	Female	66.87 ± 13
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PEP: Endoscopic retrograde cholangiopancreatography; M: Male; F: Female; NA: Not available; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

**Table 3** League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of total PEP (significant difference when OR < 1 and CI < 1)

Indomethacin+GTN	Diclofenac 100 mg	sub-GTN	Indomethacin	Diclofenac 50 mg	tra-GTN	Naproxen	Pla
0.62 (0.21, 1.82)							
0.61 (0.16, 2.38)	0.99 (0.29, 3.37)						
0.42 (0.18, 1.02)	0.69 (0.33, 1.43)	0.69 (0.23, 2.10)					
0.30 (0.07, 1.30)	0.49 (0.13, 1.86)	0.50 (0.11, 2.34)	0.72 (0.21, 2.42)				
0.30 (0.10, 0.89)	0.49 (0.20, 1.22)	0.49 (0.15, 1.66)	0.71 (0.33, 1.50)	0.99 (0.26, 3.68)			
0.26 (0.08, 0.86)	0.43 (0.17, 1.10)	0.43 (0.11, 1.62)	0.62 (0.26, 1.47)	0.86 (0.21, 3.58)	0.87 (0.30, 2.50)		
0.21 (0.09, 0.50)	0.34 (0.18, 0.65)	0.34 (0.12, 0.97)	0.49 (0.33, 0.73)	0.69 (0.22, 2.18)	0.70 (0.37, 1.32)	0.80 (0.35, 1.83)	

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate; Pla: Placebo.

**Table 4** League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of mild PEP (significant difference when OR < 1 and CI < 1)

Indomethacin+GTN	Diclofenac 100 mg	Indomethacin	tra-GTN	Naproxen	Diclofenac 50 mg	Placebo
0.59 (0.19, 1.86)						
0.46 (0.19, 1.12)	0.77 (0.35, 1.72)					
0.38 (0.12, 1.20)	0.65 (0.24, 1.75)	0.84 (0.38, 1.85)				
0.38 (0.11, 1.35)	0.64 (0.22, 1.87)	0.83 (0.32, 2.14)	0.99 (0.31, 3.14)			
0.32 (0.08, 1.39)	0.54 (0.14, 2.11)	0.70 (0.21, 2.37)	0.84 (0.22, 3.19)	0.85 (0.19, 3.71)		
0.27 (0.11, 0.67)	0.46 (0.23, 0.94)	0.59 (0.40, 0.88)	0.71 (0.36, 1.41)	0.72 (0.29, 1.78)	0.84 (0.27, 2.66)	

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.

efficacious than placebo in preventing moderate-severe PEP (Table 5). The combination of indomethacin with sublingual GTN was more efficacious than transdermal GTN (0.28, 0.09–0.85) and naproxen (0.24, 0.07–0.82) (Table 3) and was the best prevention method for moderate-severe PEP with the highest SUCRA probability (89.2%) (Figure 4C).

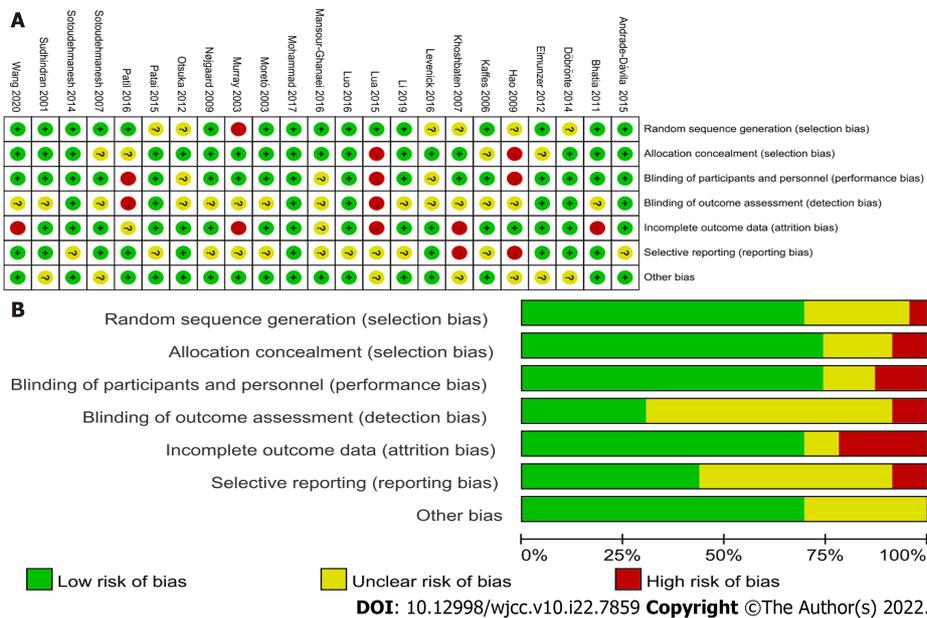
## DISCUSSION

PEP remains the most common and serious complication of ERCP. Various preventive strategies have been used to try to solve this tough problem. Common measures include pancreatic stents, pharmacotherapy, and hydration[7,35]. The prophylactic effect of pancreatic stents and rectal NSAIDs has been recognized by European clinical guidelines[6]. Nevertheless, pancreatic stents have obvious disadvantages, including injury to the pancreatic orifice and failure of placement, which significantly increases the risk of PEP. Recently, more attention has been paid to pharmacotherapy, especially NSAIDs, due to their effectiveness, cheapness and convenience. Both RCTs and meta-analyses found that rectal administration of NSAIDs was better at preventing PEP compared to oral or intramuscular

**Table 5** League table with OR estimates of each pair of interventions accompanied by 95%CI according to the prevention of moderate-to-severe PEP (significant difference when OR < 1 and CI < 1)

Indomethacin+GTN	Diclofenac 100 mg	Indomethacin	Diclofenac 50 mg	tra-GTN	Naproxen	Placebo
0.71 (0.17, 2.96)						
0.44 (0.17, 1.16)	0.61 (0.20, 1.87)					
0.47 (0.05, 4.40)	0.66 (0.07, 6.62)	1.07 (0.13, 8.55)				
0.28 (0.09, 0.85)	0.39 (0.11, 1.36)	0.63 (0.30, 1.34)	0.59 (0.07, 4.95)			
0.24 (0.07, 0.82)	0.34 (0.11, 1.02)	0.55 (0.24, 1.27)	0.52 (0.06, 4.65)	0.88 (0.32, 2.46)		
0.19 (0.08, 0.48)	0.27 (0.09, 0.79)	0.43 (0.28, 0.66)	0.41 (0.05, 3.11)	0.69 (0.37, 1.28)	0.78 (0.35, 1.77)	

GTN: Glyceryl trinitrate; sub-GTN: Sublingual glyceryl trinitrate; tra-GTN: Transdermal glyceryl trinitrate.



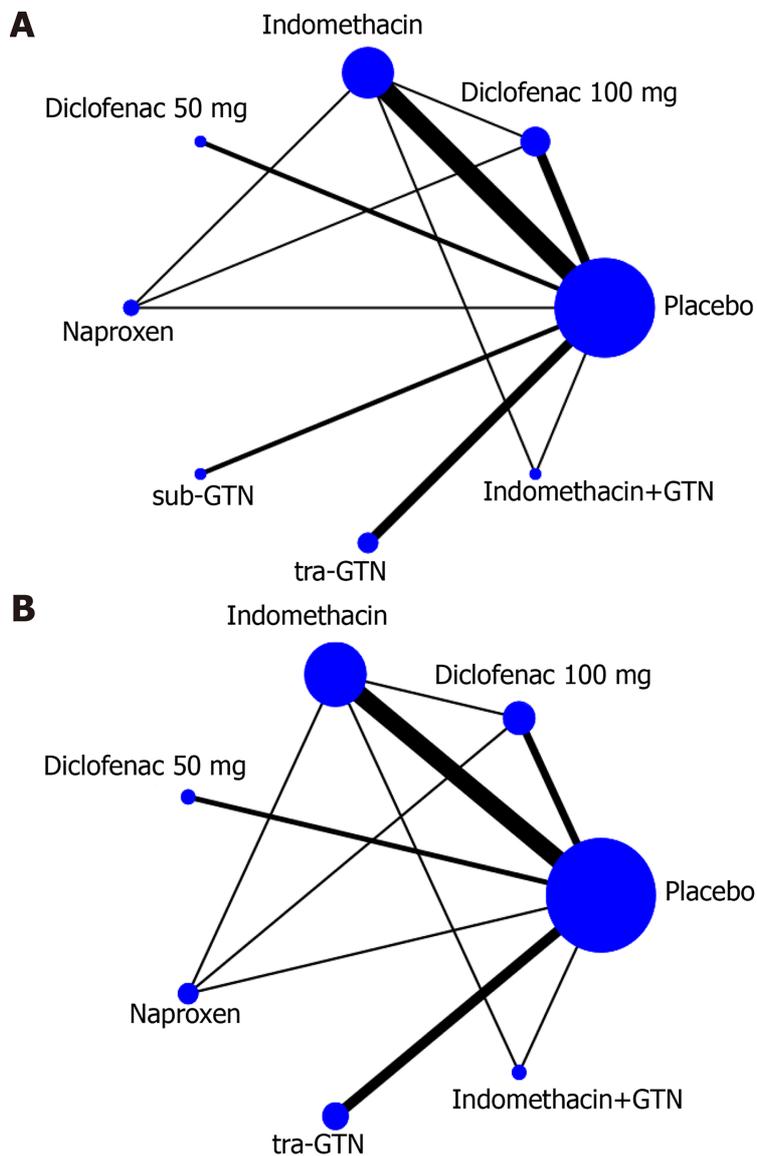
**Figure 2** Consensus risk of bias assessment of randomized control trials included in this network meta-analysis. A: Risk of bias summary; B: Risk of bias graph.

administration[7,36,37].

We did a network meta-analysis of 24 RCTs with a total of 9416 patients to identify the prophylactic efficacy of seven different interventions on PEP and to identify the best-performing dose and best route of administration. We found that rectal diclofenac 100 mg was the most effective rectal NSAID, consistent with the previous meta-analysis[7]. Sublingual GTN administration was more useful than transdermal in preventing PEP. Furthermore, the combination of indomethacin and sublingual GTN might be the best preventive strategy for PEP.

Severe PEP is a well-known complication with significant consequences for patients undergoing ERCP. Therefore, we also concentrated on this challenging complication. A network meta-analysis was also performed on 20 RCTs with a total of 8956 patients, to identify the prophylactic effect of six different interventions on mild or moderate-to-severe PEP. Since the two sublingual GTN studies did not record the severity of the PEP episodes[27,30], the preventive strategy using sublingual GTN was not included in this analysis. We found that rectal diclofenac 100 mg was also the most effective among rectal NSAIDs for preventing mild or moderate-to-severe PEP. The combination of indomethacin with sublingual GTN had the best preventive effect for mild PEP and moderate-to-severe PEP. Based on our results, rectal diclofenac 50 mg, transdermal GTN, and rectal naproxen 500 mg did not prevent or alleviate PEP better than placebo.

The exact mechanism, by which the NSAIDs prevent PEP is still a subject of debate, and there are several hypotheses. It is widely accepted that inflammatory mediators play a vital role in the pathogenesis of pancreatitis and the subsequent inflammatory response[38]. The severity of pancreatitis is also determined by the intensity of the inflammatory cascade and the systemic response. NSAIDs are potent inhibitors of phospholipase A2, which is thought to play a critical role early in the inflammatory



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**Figure 3 Network of randomized controlled trials comparison of prevention methods.** A: Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP); B: Incidence of mild or moderate-to-severe PEP.

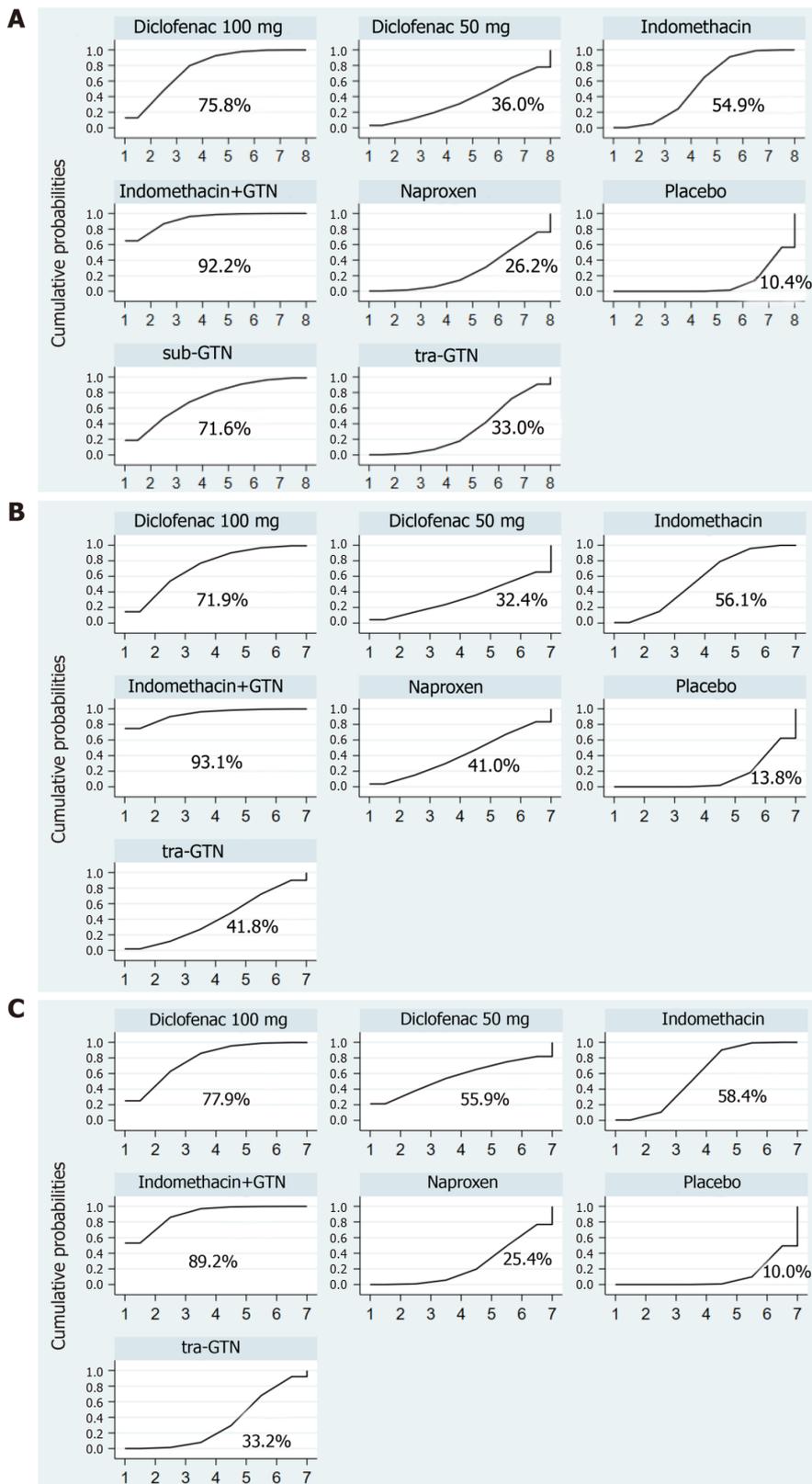
cascade[39]. This might explain the ability of NSAIDs to prevent PEP or reduce its severity.

The mechanism of GTN in preventing PEP has not been completely elucidated. The main hypothesis is that the GTN relaxes smooth muscle, which increases pancreatic parenchymal blood flow and lowers the basal pressure and contraction amplitude in the sphincter of Oddi[40]. More studies are needed to confirm the mechanism.

Despite that we believe the combination of NSAIDs with sublingual GTN might be the best preventive strategies in PEP. This analysis had some limitations. First, rectal diclofenac 100 mg is the most efficacious among rectal NSAIDs for PEP prevention, but there was no research on the combination of rectal diclofenac and sublingual GTN. There were only two studies on the combination of indomethacin and sublingual GTN[33,34], and more RCTs are needed to explore this issue in the future. Second, we only searched for RCTs published in English, which may have resulted in sample and geographical biases. Finally, few included studies had results about hyperamylasemia, post-ERCP pain, or perforation. Therefore, we could not compare these complications.

## CONCLUSION

In conclusion, this network meta-analysis confirmed that, of the NSAIDs, rectal diclofenac 100 mg was the best for PEP prophylaxis and sublingual was more effective than transdermal GTN in preventing PEP. Combination of rectal indomethacin 100 mg with sublingual GTN was the most effective strategy



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**Figure 4** Ranking of treatment strategies based on probability of prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis with the cumulative ranking area. A: Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP); B: Mild PEP; C: Moderate-to-severe PEP.

for preventing PEP and alleviating its severity. These findings help establish PEP prophylaxis for future study and practice; however, more high-quality, double-blind RCTs are needed for further network meta-analysis.

## ARTICLE HIGHLIGHTS

### Research perspectives

Clinical application of drugs.

### Research conclusions

The combination of rectal indomethacin 100 mg with sublingual glyceryl trinitrate (GTN) offered better prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) than when used alone and could alleviate the severity of PEP. This conclusion needs to be explored in more randomized controlled trials (RCTs) with large samples.

### Research results

Twenty-four eligible RCTs were selected, evaluating seven preventive strategies in 9416 patients. Rectal indomethacin 100 mg plus sublingual GTN, rectal diclofenac 100 mg, sublingual GTN, and rectal indomethacin 100 mg were all more efficacious than placebo in preventing PEP. The combination of rectal indomethacin and sublingual GTN had the highest surface under the cumulative ranking curves (SUCRA) probability of 92.2% and was the best preventive strategy for moderate-to-severe PEP with a SUCRA probability of 89.2%.

### Research methods

A systematic search was done for full-text RCTs of PEP in PubMed, Embase, Science Citation Index, and the Cochrane Controlled Trials database. Inclusion and exclusion criteria were used to screen for eligible RCTs. The major data were extracted by two independent reviewers. The Frequentist model was used to conduct this network meta-analysis and obtain the pairwise odds ratios and 95% CI.

### Research objectives

To compare NSAIDs and GTN in the prevention of PEP and to determine whether they are better in combination.

### Research motivation

To explore the role of NSAIDs and GTN for prevention of PEP.

### Research background

Post-endoscopic retrograde cholangiopancreatography pancreatitis.

## FOOTNOTES

**Author contributions:** Yang JR and Li W designed the study; Li W and Huang GX carried out critical appraisal of the included studies; Shi QQ and Ning XY performed the literature search, extracted the data; Shi QQ wrote the manuscript; Yang JR and Huang GX helped to revise the manuscript; all authors critically reviewed the manuscript and approved this study to be published.

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