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Rectal nonsteroidal anti-inflammatory drugs and pancreatic stents in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients

A network meta-analysis

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Abstract

Background: 100 mg rectal nonsteroidal anti-inflammatory drugs (NSAIDs) and pancreatic stents both significantly reduce the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Direct comparison of randomized controlled trials (RCTs) between them in high-risk patients is absent. We conducted this network meta-analysis to indirectly compare the efficacies of 100 mg rectal NSAIDs and pancreatic stents in preventing post-ERCP pancreatitis (PEP) in high-risk patients and help us decide which is preferred in clinical practice.

Methods: A comprehensive search was done to identify RCTs published in English full-text. Interventions included 100 mg rectal NSAIDs (diclofenac or indomethacin) and pancreatic stents. Only studies with high-risk patients of PEP were included. Meta-analyses of NSAIDs and pancreatic stents were conducted respectively. A network meta-analysis using the Bayesian method was performed.

Results: We included 14 RCTs, 8 on pancreatic stents and 6 on 100 mg rectal NSAIDs in high-risk patients. There was no direct comparison between them. After excluding an outlier study on NSAIDs (n = 144), meta-analyses showed they both significantly and statistically reduced the incidence of PEP in high-risk patients (pancreatic stents: n = 8 studies, random-effects risk ratio (RR)0.41, 95%CI 0.30–0.56, $I^2 = 0\%$; NSAIDs: n = 5 studies, random-effects RR 0.37, 95%CI 0.25–0.54, $I^2 = 0\%$). And network meta-analysis showed efficacy of 100 mg rectal NSAIDs was equal to pancreatic stents (random-effects RR 0.94, 95%CI 0.50–1.8).

Conclusions: The efficacy of 100 mg rectal NSAIDs (diclofenac or indomethacin) seems equally significant to pancreatic stents in preventing PEP in high-risk patients. Considering the cost-effectiveness and safety, 100 mg diclofenac or indomethacin may be preferred.

Abbreviations: CI = confidence interval, ERCP = endoscopic retrograde cholangiopancreatography, ESGE = European Society of Gastrointestinal Endoscopy, GRADE = Grading of Recommendations Assessment, Development and Evaluation NSAID: nonsteroidal anti-inflammatory drug, PEP = post-ERCP pancreatitis, PS = pancreatic stenting/stent, RCT = randomized controlled trial, RR = risk ratio.

Keywords: diclofenac, endoscopic retrograde cholangiopancreatography, indomethacin, meta-analysis, nonsteroidal anti-inflammatory drug, pancreatic stents, pancreatitis

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1. Introduction

It is widely accepted that endoscopic retrograde cholangiopancreatography (ERCP) plays an important role in the investigation and treatment of biliary and pancreatic diseases. Post-ERCP pancreatitis (PEP) is the most common major complication. It is usually defined as "new or worsened abdominal pain combined with > 3 times the normal value of amylase or lipase at more than 24 hours after ERCP and requirement of admission or prolongation of a planned admission."[1] The incidence of PEP reported ranges from 3.5% to 9.7% in average-risk patients and as high as 25% to 70%[2] in high-risk patients, which related to risk factors on patient, procedure and endoscopist. Patient-related risk factors include suspected sphincter of Oddi dysfunction, female sex, previous pancreatitis, previous PEP, younger age, nondilated extrahepatic bile duct, absence of chronic pancreatitis, normal serum bilirubin, end-stage renal disease.[1] Procedure-related risk factors include difficult cannulation, pancreatic guidewire passages > 1, pancreatic injection, precut sphincterotomy, pancreatic sphincterotomy, biliary balloon sphincter dilation, failure to clear bile duct stones, intraductal ultrasound.[1] PEP is mostly mild and only 0.1% to 0.7% of patients die from PEP.[1] However, due to the wide application of ERCP, the total number of patients with PEP is large, which adds a heavy burden to patients and the society.

Mechanisms of PEP may contain impaired pancreatic duct drainage, activation of prostaglandin and prostacyclin cascades, and pancreatic tissue ischemia.[3] Though many strategies including pancreatic stent, allopurinol, diclofenac, indomethacin, octreotide,somatostatin, gabexate, glyceryl trinitrate, ulinastatin, and nafamostat have been reported to prevent PEP or reduce the severity of PEP, the updated European Society of Gastrointestinal Endoscopy (ESGE) guideline only strongly recommends rectal administration of 100 mg diclofenac or indomethacin in all patients, aggressive hydration with lactated Ringer's solution in patients with contraindication to nonsteroidal anti-inflammatory drugs (NSAIDs), and prophylactic pancreatic stenting in selected high risk patients for PEP. Pancreatic stenting (PS) maintains pancreatic drainage, and rectal NSAIDs may inhibit the activation of prostaglandin and prostacyclin cascades. Several recent studies indicated the combination of rectal NSAIDs and PS did not add benefit compared with rectal NSAIDs or PS alone.[3–6] So which better prevents PEP in patients at high risk for PEP remains a question considering the cost-effectiveness and rectal NSAIDs' notable efficacy in average-risk patients. In the absence of direct comparison of randomized controlled trial (RCTs) between 100 mg rectal NSAIDs (diclofenac or indomethacin) and PS, we performed this network meta-analysis. We hope it can clarify the role of rectal NSAIDs and PS in reducing the risk of PEP in high-risk patients and help us decide which is preferred in clinical practise.

2. Materials and methods

2.1. Protocol

The meta-analysis was performed according to the recommendations of the Cochrane Handbook and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org/PRISMAStatement/) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analyses (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis). Ethical approval was not provided because this study was conducted by including published studies.

2.2. Search strategy

A comprehensive search was conducted independently by 2 authors in PubMed, Embase, Cochrane Library Central up to January 12, 2020. The search terms included "ERCP, endoscopic retrograde cholangiopancreatography, pancreatitis, NSAIDs, nonsteroidal anti-inflammatory drugs, diclofenac, indomethacin, and stent. RCT filters were incorporated into the search strategy.

2.3. Inclusion and exclusion criteria

The studies were selected when meeting all of the following criteria:

(1) human RCTs comparing the incidence of PEP between 100 mg rectal NSAID (diclofenac or indomethacin) or PS and placebo or no treatment;
(2) Studies enrolling patients at high-risk of PEP;
(3) Full-length English articles.

We excluded the studies meeting any of the following criteria:

(1) Non-RCT;
(2) Studies on oral or intravenous or intramuscular NSAID and other NSAIDs such as ketoprofen, naproxen, valdecoxib, flurbiprofen;
(3) Studies enrolling patients at low-risk or average-risk of PEP.

2.4. Data extraction

Two authors extracted independently the original data such as the first author, publication year, country, sample size, types of NSAIDs, drug dose, type of PS, and the incidence of PEP in each group. We contacted the author of the article to obtain original data when needed, and excluded the study if missing data could not be obtained. Conflicts in data extraction were resolved by a consensus.

2.5. Risk of bias assessment

Two authors assessed independently the quality of the studies using the Cochrane Collaboration's 'Risk of Bias' tool 2.0.[7] Conflicts were resolved by a consensus.

2.6. Statistical analysis

Meta-analyses of NSAIDs and PS were performed by using the Review Manager (RevMan) version 5.3 software. Risk ratio (RR) with a 95% confidence interval (CI) were used to describe dichotomous outcomes. A random-effects model was used to pool the results. The heterogeneity among studies was evaluated by Cochran Q statistical test and Higgin test (I^2). $P < .1$ was considered as statistical significance. The interpretation of I^2 was as follows: 0% to 40% indicated heterogeneity might not be important; 30% to 60% might be moderate heterogeneity; 50% to 90% might represent substantial heterogeneity; 75% to 100% represented considerable heterogeneity. A sensitivity analysis was conducted if needed. A funnel plot analysis was performed to assess publication bias. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to summarize the findings. The network meta-analysis of

Table 1

Summary characteristics of included studies on pancreatic stents.

Ref.	Year	Country	Sample size no stent (n)	Sample size Stent (n)	Total (n)	Types of pancreatic stent
Ito[39]	2010	Japan	35	35	70	5fr, 4 cm with a single duodenal pig tail
Kawaguchi[40]	2012	Japan	60	60	120	5fr, 3 cm with two flanges on the duodenal side
Lee[41]	2012	South Korea	51	50	101	unflanged 3fr, 4, 6, or 8 cm duodenal pig tail stent
Pan[2]	2011	China	20	20	40	5fr single pig tail
Phillip[42]	2019	Europe	80	87	167	5 French plastic pancreatic stent of various length
Sofuni[43]	2011	Japan	204	203	407	5Fr, 3 cm with 2 flanges on the duodenal side
Tarnasky[44]	1998	USA	39	41	80	5 or 7Fr, 2 or 2.5 cm
Yin[45]	2016	China	102	104	206	5Fr, 5, 7, or 9 cm

indirect evidence using the Bayesian method was performed using JAGS, RStudio, R (version: x64 3.6.2) with the gemtc package with a random-effect model.

3. Results

3.1. Selected study and characteristics of the trials

We identified 1740 records through database searching and excluded 237 duplicate articles. We retrieved the titles and abstracts of the remaining 1503 records and left 32 articles which met the selection criteria. From the 32 articles, 2 studies on low dose (50 mg) rectal diclofenac were excluded.[8,9] A study comparing pharmacological prophylaxis and pancreatic duct stenting plus pharmacological prophylaxis was excluded.[3] A study was excluded because PEP was defined in the study by "abdominal pain with elevated serum lipase or amylase no less than 2 times the normal upper limit",[10] which was loose compared with the usual definition (abdominal pain with elevated serum lipase more than 3 times the normal upper limit) and probably produced a higher incidence of PEP. Seven studies enrolling patients at low-risk or average-risk of PEP were excluded.[11–17] Six retrospective studies were excluded.[4,6,18–21] A study on rectal indomethacin in high-risk population was excluded because >80 of the patients compared received a prophylactic pancreatic stent because the endoscopist deemed the case high-risk to merit a pancreatic stent.[22] We also contacted the author of a study[23] to obtain the detailed data we needed in the meta-analysis. Finally, 14 RCTs including 8 on PS versus no stent and 6 on 100 mg rectal NSAIDs versus placebo in patients at high-risk of PEP were included in the network meta-analysis (Tables 1 and 2). Notably, there was no direct comparison between 100 mg rectal NSAIDs (diclofenac or indomethacin) and PS in high-risk patients. The selection process is shown in Figure 1.

3.2. Methodological quality and risk of bias

Two authors evaluated methodological quality of the studies using the Cochrane Collaboration's 'Risk of Bias' tool 2.0. Each study was given a summary assessment of low, unclear, or high risk of bias. Overview of methodological quality of the studies included on pancreatic stent and rectal NSAIDs were presented in Figures 2 and 3.

3.3. Efficacy of PS(comparison with no stent)

As show in Figure 4, PEP occurred in 48 (8.00%) patients who underwent pancreatic stenting, and 124 (20.98%) patients who did not. The heterogeneity was low ($I^2=0\%$, $P=.49$). The incidence of PEP was significantly reduced in patients who underwent pancreatic stenting than in the patients who did not (RR = 0.41; 95%CI: 0.30–0.56) with a moderate GRADE of evidence (Fig. 5). We did not perform a funnel plot analysis since publication bias could not be assessed with acceptable certainty in case of less than 10 studies.

3.4. Efficacy of 100 mg rectal NSAIDs (comparison with placebo)

As show in Figure 6, PEP occurred in 39 (6.76%) patients who underwent 100 mg rectal NSAID administration, and 98 (16.36%) patients who did not. The heterogeneity was moderate ($I^2=48\%$, $P=.09$). An outlier was identified from the forest plot. We reassessed the study and found it had some limitations. We excluded it (Lua 2015[24]) and ran another analysis (Fig. 7). The heterogeneity of new analysis was very low ($I^2=0\%$, $P=.57$) The incidence of PEP was significantly and statistically reduced in patients who underwent 100 mg rectal NSAID administration than the patients who did not (RR = 0.37; 95%CI: 0.25–0.54) with a moderate GRADE of evidence (Fig. 8). We did not perform a funnel plot analysis since publication bias could not be assessed with acceptable certainty in case of less than 10 studies.

Table 2

Summary characteristics of included studies on rectal NSAIDs.

Ref.	Year	Country	Sample size Placebo (n)	Sample size NSAIDs (n)	Total (n)	Types of NSAIDs
Andrade-Dávila[46]	2015	Mexico	84	82	166	100 mg rectal indomethacin immediately after ERCP
Elmunzer[47]	2013	USA	58	48	106	100 mg rectal indomethacin immediately after ERCP
Khoshbaten[48]	2008	Iran	50	50	100	100 mg rectal diclofenac immediately after ERCP
Lua[24]	2015	Malaysia	75	69	144	100 mg rectal diclofenac immediately after ERCP
Murray[49]	2003	Scotland	110	110	220	100 mg rectal diclofenac immediately after ERCP
Patai[23]	2015	Hungary	222	218	440	100 mg rectal indomethacin within 1 h before ERCP

ERCP = endoscopic retrograde cholangiopancreatography, NSAIDs = nonsteroidal anti-inflammatory drugs.

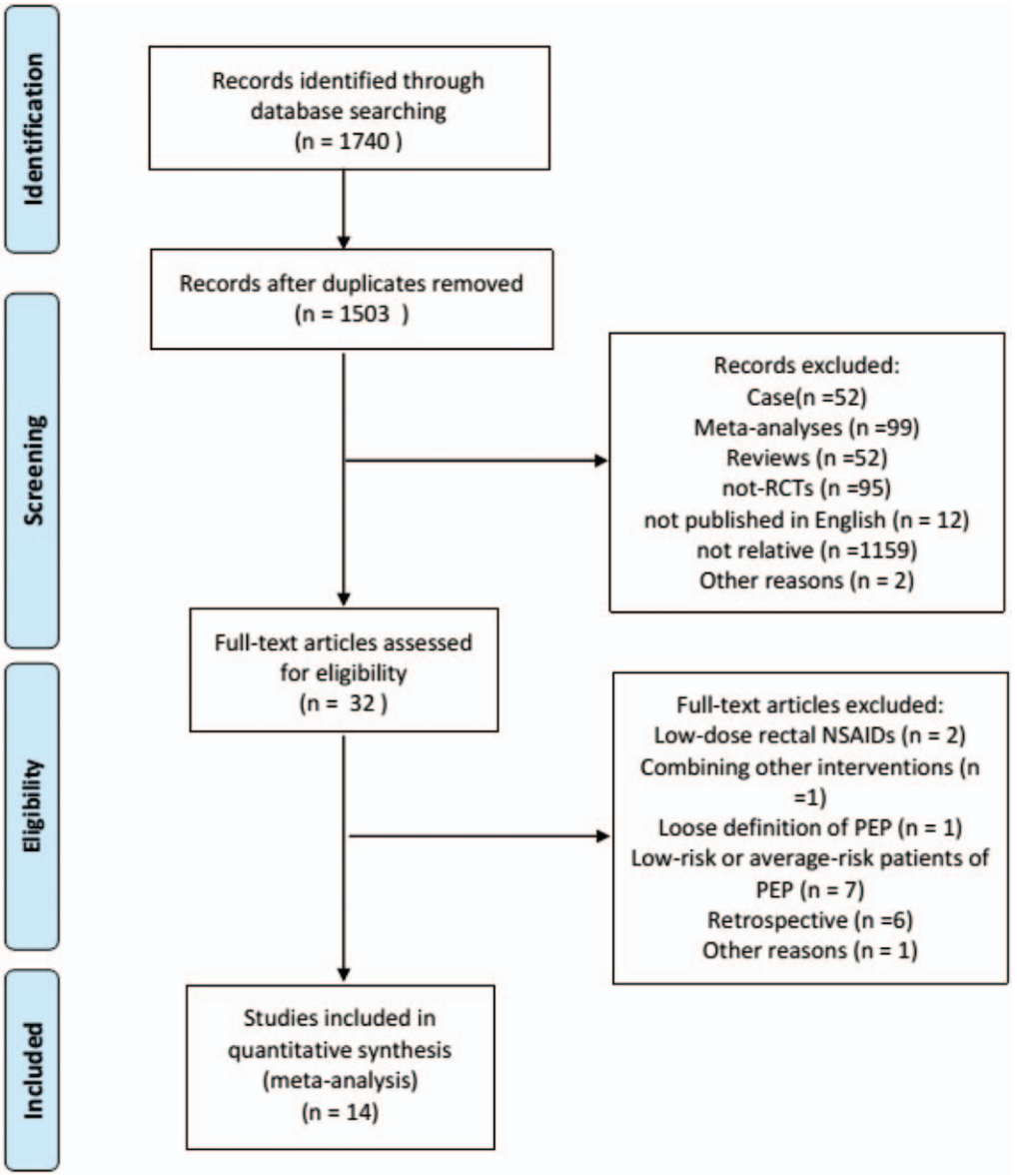

Figure 1. Flowchart of the selection process.

3.5. Comparative effectiveness

A network meta-analysis without the outlier study above[24] using the Bayesian method were performed using R with the gemtc package with a random-effect model. A network graph of the included studies is presented in Figure 9. There was no direct comparison of RCTs between 100 mg rectal NSAIDs (diclofenac or indomethacin) and PS. We found the efficacy of 100 mg rectal NSAID was equal to pancreatic stents (random-effects RR 0.94, 95%CI 0.50–1.8) (Table 3).

4. Discussion

PS placement has been used to prevent PEP for a long time. Meta-analyses reported that prophylactic PS was beneficial in unselected as well as average-risk and high-risk patients.[25–27] PS placement is really challenging because it can induce injury to the pancreatic orifice and failure of placement actually increases risk of PEP. In recent years, rectal NSAIDs were proved to be effective in average-risk and high-risk patients.[28,29] Rectal NSAIDs are cheap and of low risk. Meta-analyses showed that the overall rates of adverse events in the NSAIDs groups versus control groups were found no significant difference, as well as the specific complications such as gastrointestinal bleeding, renal dysfunctions and anal itching.[1] NSAIDs might cause fatal allergic and pseudoallergic reactions (Stevens–Johnson and Lyell's syndromes) but they are extremely rare.[1] ESGE recommends against prophylaxis of NSAIDs in patients and first-degree relatives with a history of Stevens–Johnson or Lyell's syndromes caused by NSAIDs.[1] Considering the fetal risks of complications such as premature closure of ductus arteriosus, prophylaxis of NSAIDs in women at more than 30-week gestation should be avoided.[1] Besides, it seems to be a tempting prophylactic method for PEP. Notably, several recent studies indicated the combination of rectal NSAIDs and PS did not add benefit compared with rectal NSAIDs or PS alone.[3–6] So we performed this network meta-analysis to

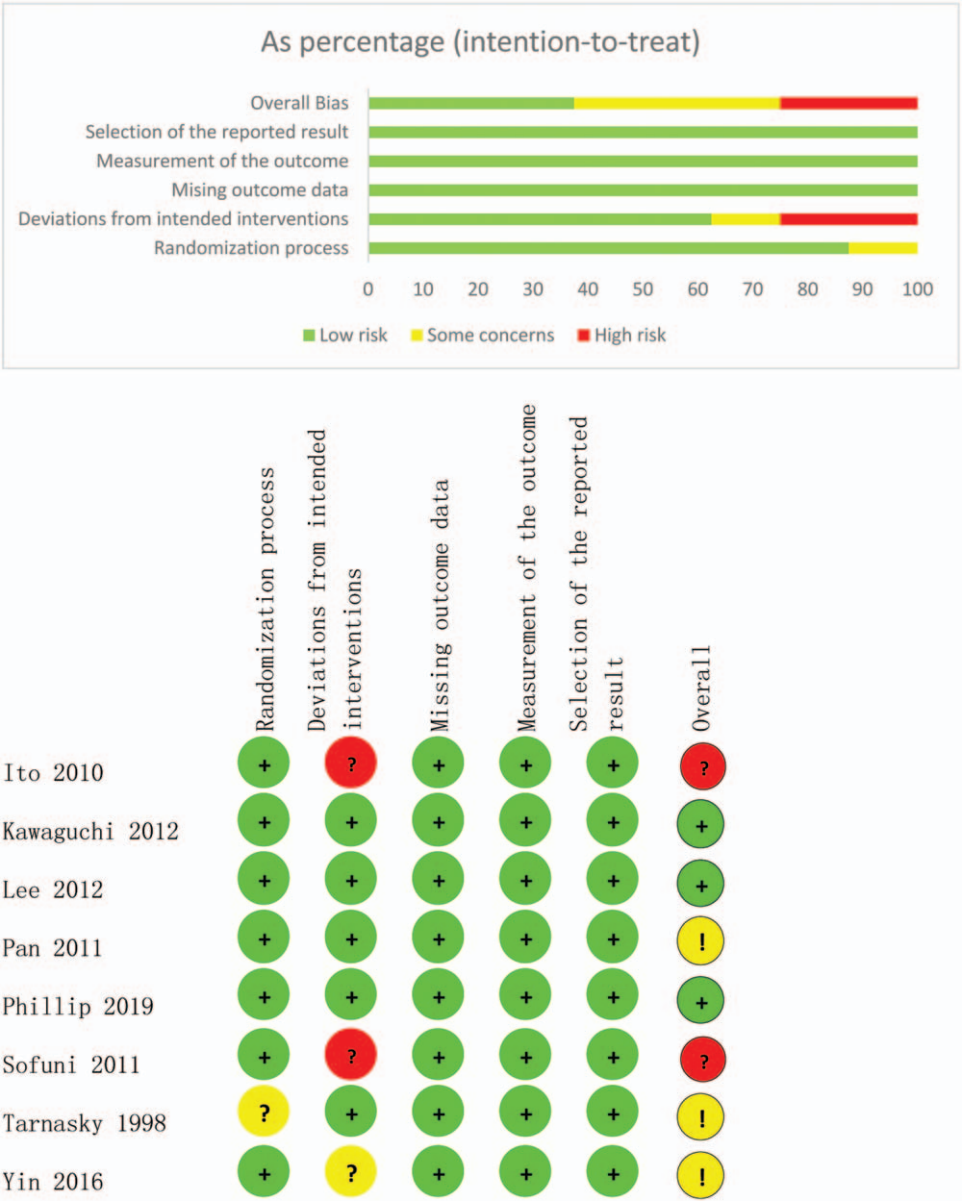

Figure 2. Consensus risk of bias assessment of the included studies on pancreatic stent. Green, low risk; yellow, unclear; red, high risk.

compare the efficacies of two prophylactic methods and identify the better one.

There were several important points in the study selection. First is the definition of PEP. It is usually defined as abdominal pain combined with elevation of serum amylase or lipase > 3 times the normal value, so we excluded a study in the selection in case of a higher incidence of PEP due to its definition of PEP with elevated serum lipase or amylase more than 2 times the normal value.[10] Second is the definition of high-risk. The updated ESGE Guideline suggests that patients with at least 1 definite or 2 likely patient-related or procedure-related risk factors should be considered to be at high risk for PEP.[1] The criterion of high-risk patients used in the original studies were very close. We excluded the studies on low-risk and average-risk patients because rectal NSAIDs were proved to be easy to use, cheap, effective, and of low risk in these patients. Third is that NSAIDs should be 100 mg diclofenac or indomethacin. Meta-analyses showed that only the rectal route was effective among the various routes of NSAID administration.[1] Diclofenac and indomethacin were the most frequent and effective NSAIDs, and the most frequent dosage was 100 mg for both drugs in the RCTs included.[28,30,31] The efficacy of low-dose rectal NSAIDs is controversial.[8,9] Other NSAIDs such as ketoprofen and valdecoxib are probably not effective.[31] The timing of rectal administration of NSAIDs may also make a difference. The findings of meta-analyses which suggested a higher efficacy of NSAIDs before or after ERCP were affected by factors such as the numbers of included studies other than drug efficacy.[1] The number of studies included in our meta-analysis were 6, only 1 of which was within 1 h before ERCP and others were immediately after ERCP, so we did not perform the subgroup

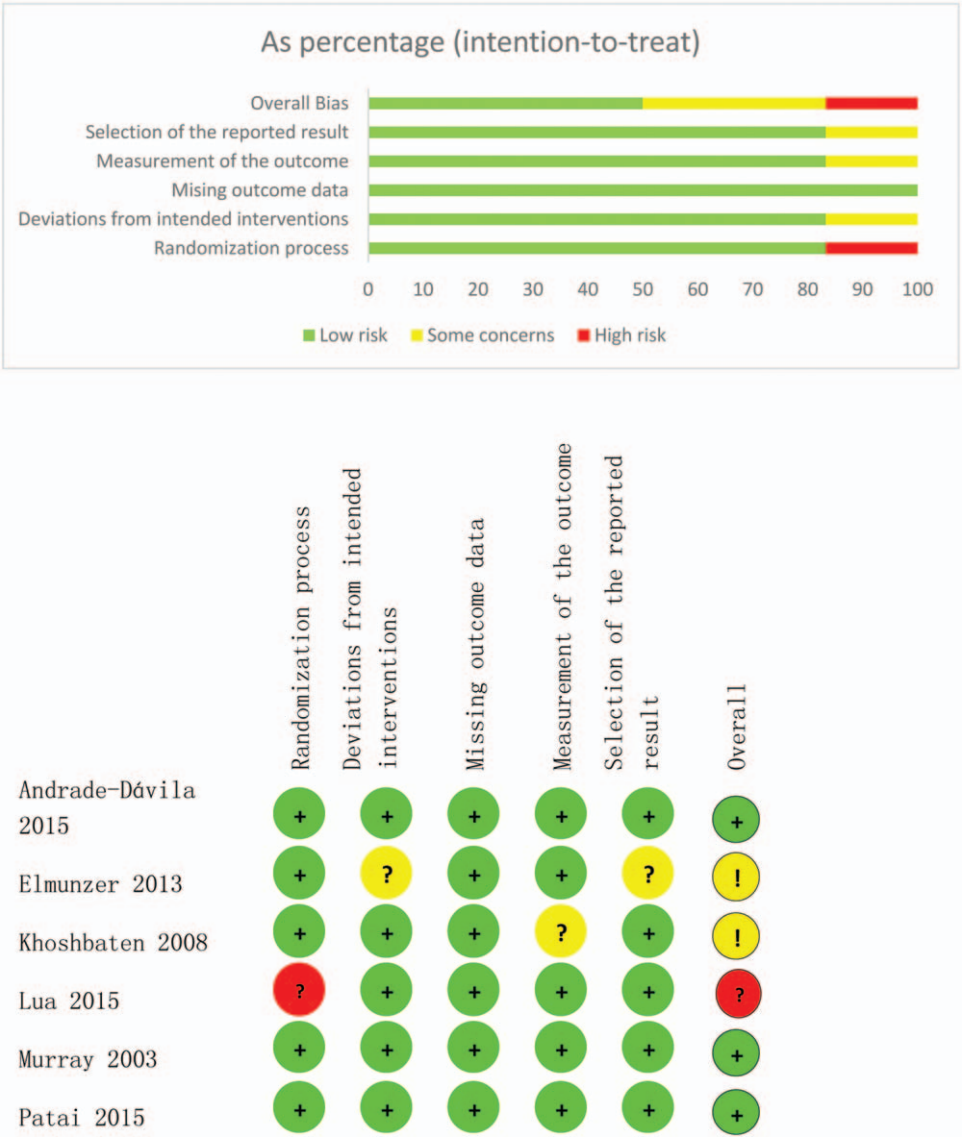

Figure 3. Consensus risk of bias assessment of the included studies on rectal nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin). Green, low risk; yellow, unclear; red, high risk.

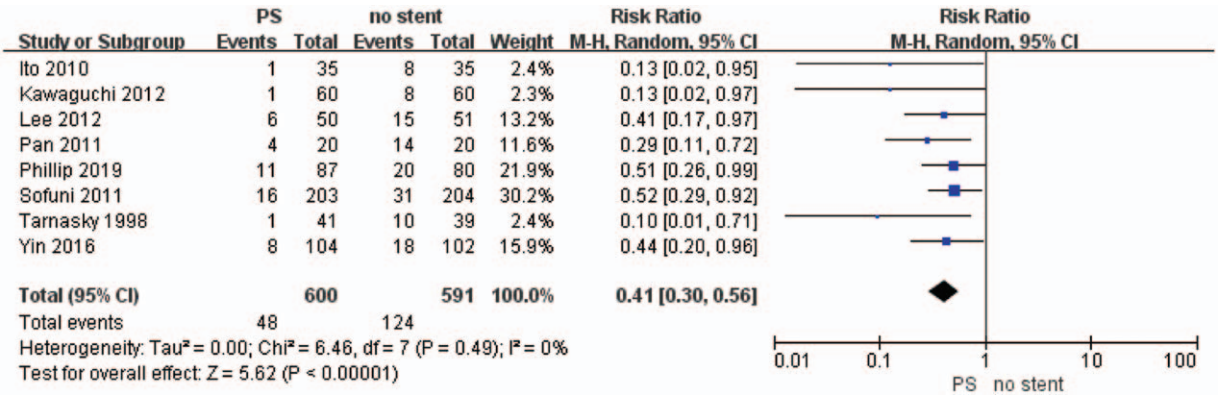

Figure 4. Forest plot of comparison of incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis between pancreatic stent and no stent in high-risk patients. PS = pancreatic stent.

pancreatic stent for high-risk patients of post-ERCP pancreatitis

Patient or population: high-risk patients of post-ERCP pancreatitis
Settings:
Intervention: pancreatic stent

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Pancreatic stent	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
incidence of post-ERCP pancreatitis	Study population		RR 0.41 (0.3 to 0.56)	1191 (8 studies)	⊕⊕⊕⊖ moderate[1]	
	210 per 1000	86 per 1000 (63 to 117)				
	Moderate					
	239 per 1000	98 per 1000 (72 to 134)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unsuccessful pancreatic duct stenting likely caused deviations from intended interventions in three studies.

Figure 5. Pancreatic stent significantly reduced the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients with a moderate GRADE of evidence. ERCP = endoscopic retrograde cholangiopancreatography, GRADE = Grading of Recommendations Assessment, Development and Evaluation.

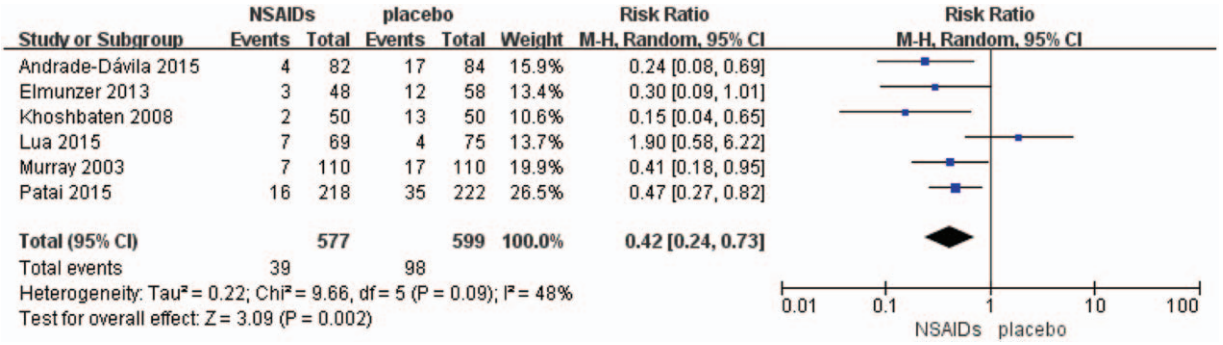

Figure 6. Forest plot of comparison of incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis between 100 mg rectal nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin) and placebo in high-risk patients. NSAIDs = nonsteroidal anti-inflammatory drugs.

meta-analysis based on different timing of administration of NSAIDs.

We included 14 randomized clinical trials, 8 on PS versus no stent and 6 on 100 mg rectal NSAIDs versus placebo in patients with high-risk of PEP. There was no direct comparison between 100 mg rectal NSAIDs (diclofenac or indomethacin) and PS in high-risk patients. Meta-analyses showed that both 100 mg rectal NSAIDs and PS alone significantly and statistically lower the

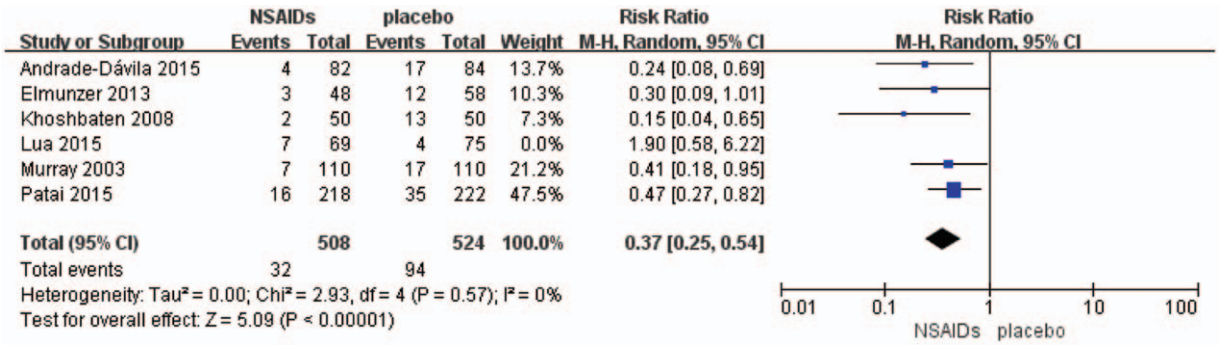

Figure 7. Forest plot of comparison of incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis between 100 mg rectal nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin) and placebo in high-risk patients after excluding the outlier study. NSAIDs = nonsteroidal anti-inflammatory drugs.

NSAIDs for high-risk patients of post-ERCP pancreatitis

Patient or population: high-risk patients of post-ERCP pancreatitis
Settings:
Intervention: NSAIDs

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk NSAIDs	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
incidence of post-ERCP pancreatitis	Study population		RR 0.37 (0.25 to 0.54)	1032 (5 studies)	⊕⊕⊕⊕ moderate[1,2]	
	179 per 1000	66 per 1000 (45 to 97)				
	Moderate					
	180 per 1000	67 per 1000 (45 to 97)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Placement of a pancreatic stent might caused deviations from intended interventions.
[2] A more stringent diagnostic criterion for post-ERCP pancreatitis than usual was used in a study.

Figure 8. Nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin) significantly reduced the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients with a moderate GRADE of evidence. ERCP = endoscopic retrograde cholangiopancreatography, GRADE = Grading of Recommendations Assessment, Development and Evaluation, NSAIDs = nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin).

incidence of PEP in high-risk populations with a moderate GRADE of evidence. The network meta-analysis showed efficacy of 100 mg rectal NSAIDs was equal to PS. Considering the cost-effectiveness and safety, 100 mg diclofenac or indomethacin may be better.

The heterogeneity across the 8 trials on PS was very low. But the heterogeneity across the 6 trials on NSAIDs was moderate ($I^2 = 48\%$, $P = .09$). Further analysis of the outlier study indicated several limitations of the study. First, it was a single-blinded design. Second, 7 of 151 patients were excluded because they were lost during the follow up, and the characteristics such as female sex, dilated ducts, pancreatography, placement of pancreatic stent in the rest patients of diclofenac group and control group were different. Notably, pancreatic stents were placed in 4 cases of the diclofenac group (5.8%) as a prophylactic measure of PEP and not in the control group. Among these 4 cases, 2 developed PEP.[24] Third, the overall incidence of PEP in the study was much lower than other studies in high-risk patients and the sample size was not adequate to generate statistical power due to the low incidence of PEP. Considering these we excluded it and ran another analysis. The heterogeneity of new analysis was very low ($I^2 = 0\%$, $P = .57$).

This study has some limitations. First, all RCTs involved in this study were full-texts written in English. Second, the number of included studies was small and publication bias might existed. Third, the type of PS was not exactly same among the RCTs. Stents of 5-Fr diameter were found to be more efficacious than 3-Fr stents and stent length of 3 cm might be superior to 5 cm[1]. An internal flange could facilitate spontaneous elimination and a duodenal pigtail or flange could prevent intraductal migration. Fourth, secondary outcome measures such as the proportion of patients in each group with moderate and severe PEP and treatment-related adverse events were not reported in our study, which may limit clinical application of these measures.

Our network meta-analysis is better than other 2 network meta-analyses comparing the efficacies of rectal NSAIDs (diclofenac or indomethacin) and PS in high-risk patients in terms of quality of evidence. The network meta-analysis in

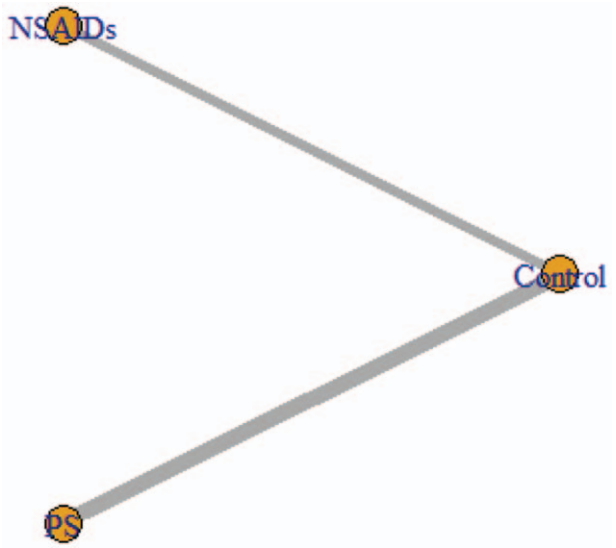

Figure 9. Network graph of the included studies. The thicknesses of the lines represented the number of comparisons. NSAIDs, nonsteroidal anti-inflammatory drugs (diclofenac or indomethacin); PS, pancreatic stent.

Table 3

Network meta-analysis without the outlier study.

Comparison	RR	95% CI
NSAIDs vs Control	0.32	0.18–0.51
PS vs Control	0.34	0.21–0.49
NSAIDs vs PS	0.94	0.50–1.8

CI = confidence Interval, NSAIDs = nonsteroidal anti-inflammatory drugs, PS = pancreatic stents, RR = risk ratio.

2013[25] mixed several observational studies in RCTs. And it only included 2 studies comparing NSAIDs with placebo in high-risk patients and examined the efficacies of rectal NSAIDs and PS among mixed average-risk and high-risk cohorts. And the recent network meta-analysis[32] mixed with 4 studies[12,13,16,33] in unselected patients in the rectal NSAIDs group and 1 study[9] on low-dose rectal NSAID. One study[34] included on NSAID was published in Hungarian and was one part of another study included.[13] One study[35] on prophylactic PS for endoscopic snare excision of duodenal ampulla should be abandoned because the procedure greatly changed the form of the Vater papilla and the sample size was only 19. Two studies[10,36] which defined PEP with a lower criterion (serum lipase or amylase more than 2 times the normal upper limit) were also included improperly.

Though patients enrolled in the RCTs included in our analyses were all at high-risk of PEP, there may still have been substantial difference in the baseline risks among the RCTs. So we expect an accumulation of RCTs directly comparing 100 mg rectal NSAIDs and PS in high-risk populations besides the 2 actively recruiting clinical trials.[37,38] Furthermore, NSAIDs cannot eliminate the risk of PEP, PS may still be important in the patients with some specific risk factors which need to be explored.

5. Conclusions

The efficacy of 100 mg rectal NSAIDs (diclofenac or indomethacin) seems equally significant to pancreatic stents in preventing PEP in high-risk patients. Considering the cost-effectiveness and safety, 100 mg diclofenac or indomethacin may be preferred.

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Author contributions

Conceptualization: Yin Shou-xin, Han Shuai
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References

[1] Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2020;52:127–49.
[2] Pan XP, Dang T, Meng XM, et al. Clinical study on the prevention of post-ERCP pancreatitis by pancreatic duct stenting. Cell Biochem Biophys 2011;61:473–9.
[3] Sotoudehmanesh R, Ali-Asgari A, Khatibian M, et al. Pharmacological prophylaxis versus pancreatic duct stenting plus pharmacological prophylaxis for prevention of post-ERCP pancreatitis in high risk patients: a randomized trial. Endoscopy 2019;51:915–21.
[4] Siddiqui AA, Patel D, Kaplan J, et al. A trial of rectal indomethacin to prevent post-ercp pancreatitis in patients with suspected type 3 sphincter of oddi dysfunction. Dig Dis Sci 2015;60:2509–15.
[5] Lang GD, Fejleh P, Bhat T, et al. No added benefit of indomethacin in the prevention of post-ercp pancreatitis after protective pancreatic duct stent placement in low risk patients. Gastrointest Endosc 2016;83:AB248.
[6] Abdelfatah MM, Gochanour E, Koutlas NJ, et al. Post-endoscopic retrograde cholangiopancreatography pancreatitis: single versus dual prophylactic modalities. Pancreas 2019;48:e24.
[7] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[8] Katoh T, Kawashima K, Fukuba N, et al. Low-dose rectal diclofenac does not prevent post-ERCP pancreatitis in low- or high-risk patients. J Gastroenterol Hepatol 2019;35:1247–53.
[9] Otsuka T, Kawazoe S, Nakashita S, et al. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial. J Gastroenterol 2012;47: 912–7.
[10] Fazel A, Quadri A, Catalano MF, et al. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc 2003;57:291–4.
[11] Montaño Loza A, Rodríguez Lomelí X, García Correa JE, et al. Effect of the rectal administration of indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes. Revista Espanola de Enfermedades Digestivas 2007;99:330–6.
[12] Sotoudehmanesh R, Khatibian M, Kolahdoozan S, et al. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007;102:978–83.
[13] Döbrönte Z, Szepes Z, Izbéki F, et al. Is rectal indomethacin effective in preventing of post-endoscopic retrograde cholangiopancreatography pancreatitis? World J Gastroenterol 2014;20:10151–7.
[14] Shafique MS, Khan JS, Fayyaz MU, et al. Prophylactic rectal NSAIDS in the prevention of POST-ERCP pancreatitis. Postgrad Med J 2016; 30:184–8.
[15] Sofuni A, Maguchi H, Itoi T, et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol 2007;5:1339–46.
[16] Levenick JM, Gordon SR, Fadden LL, et al. Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients. Gastroenterology 2016;150:911–7.
[17] Tsuchiya T, Itoi T, Sofuni A, et al. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center. J Hepatobiliary Pancreat Surg 2007;14: 302–7.
[18] Ang TL, Kwek ABE, Song M, et al. Comparative study of strategies for preventing post-ERCP pancreatitis after early precut sphincterotomy for biliary access. J Dig Dis 2016;17:692–6.
[19] Leerhøy B, Nordholm-Carstensen A, Novovic S, et al. Diclofenac is associated with a reduced incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis results from a danish cohort study. Pancreas 2014;43:1286–90.
[20] Li GD, Jia XY, Dong HY, et al. Pancreatic stent or rectal indomethacin-which better prevents post-ERCP pancreatitis: a propensity score matching analysis. Medicine (United States) 2016;95:
[21] Thiruvengadam NR, Forde KA, Ma GK, et al. Rectal indomethacin reduces pancreatitis in high- and low-risk patients undergoing endoscopic retrograde cholangiopancreatography. Gastroenterology 2016;151:288–97e284.
[22] Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414–22.
[23] Patai A, Solymosi N, Patai ÁV. Effect of rectal indomethacin for preventing post-ERCP pancreatitis depends on difficulties of cannulation. J Clin Gastroenterol 2015;49:429–37.
[24] Lua GW, Muthukaruppan R, Menon J. Can rectal diclofenac prevent post endoscopic retrograde cholangiopancreatography pancreatitis? Dig Dis Sci 2015;60:3118–23.
[25] Akbar A, Abu Dayyeh BK, Baron TH, et al. Rectal nonsteroidal anti-inflammatory drugs are superior to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a network meta-analysis. Clin Gastroenterol Hepatol 2013;11:778–83.
[26] Vadalà Di Prampero SF, Faleschini G, Panic N, et al. Endoscopic and pharmacological treatment for prophylaxis against postendoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis and systematic review. Eur J Gastroenterol Hepatol 2016;28:1415–24.

[27] Mazaki T, Mado K, Masuda H, et al. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol 2014;49:343–55.
[28] Yaghoobi M, Alzahrani MA, McNabb-Baltar J, et al. Rectal indomethacin prevents moderate to severe post-ERCP pancreatitis and death and should be used before the procedure: A meta-analysis of aggregate subgroup data. J Can Assoc Gastroenterol 2018;1:67–75.
[29] Lyu Y, Cheng Y, Wang B, et al. What is impact of nonsteroidal anti-inflammatory drugs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2018;18:106.
[30] Liu L, Li C, Huang Y, et al. Nonsteroidal anti-inflammatory drugs for endoscopic retrograde cholangiopancreatography postoperative pancreatitis prevention: a Systematic Review and meta-analysis. J Gastrointest Surg 2019;23:1991–2001.
[31] Serrano JPR, De Moura DTH, Bernardo WM, et al. Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Endosc Int Open 2019;7:E477–86.
[32] Njei B, McCarty T R, Muniraj T, et al. Comparative effectiveness of pharmacologic and endoscopic interventions for prevention of post-ERCP pancreatitis: a network meta-analysis. Endosc Int Open. 2020;8: E29–40.
[33] Ucar R, Biyik M, Ucar E, et al. Rectal or intramuscular diclofenac reduces the incidence of pancreatitis afterendoscopic retrograde cholangiopancreatography. Turk J Med Sci 2016;46:1059–63.
[34] Döbrönte Z, Toldy E, Márk L, et al. Effects of rectal indomethacin in the prevention of post-ERCP pancreatitis. Orvosi Hetilap 2012;153:990–6.
[35] Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc 2005; 62:367–70.
[36] Smithline A, Silverman W, Rogers D, et al. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. Gastrointest Endosc 1993;39:652–7.
[37] ClinicalTrials.gov, Comparative Effectiveness Between Rectally Administered Indomethacin and Pancreatic Stenting in the Prevention of Post ERCP Pancreatitis, https://clinicaltrialsgov/show/NCT03713879 2018.
[38] Elmunzer BJ, Serrano J, Chak A, et al. Rectal indomethacin alone versus indomethacin and prophylactic pancreatic stent placement for preventing pancreatitis after ERCP: study protocol for a randomized controlled trial. Trials. 2016;17:120.
[39] Ito K, Fujita N, Noda Y, et al. Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial. J Gastroenterol 2010;45:1183–91.
[40] Kawaguchi Y, Ogawa M, Omata F, et al. Randomized controlled trial of pancreatic stenting to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. World J Gastroenterol 2012;18:1635–41.
[41] Lee TH, Moon JH, Choi HJ, et al. Prophylactic temporary 3F pancreatic duct stent to prevent post-ERCP pancreatitis in patients with a difficult biliary cannulation: A multicenter, prospective, randomized study. Gastrointest Endosc 2012;76:578–85.
[42] Philip V, Pukitis A, Epstein A, et al. Pancreatic stenting to prevent post-ERCP pancreatitis: A randomized multicenter trial. Endosc Int Open 2019;7:E860–8.
[43] Sofuni A, Maguchi H, Mukai T, et al. Endoscopic pancreatic duct stents reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. Clin Gastroenterol Hepatol 2011;9:851–8.
[44] Tarnasky PR, Palesch YY, Cunningham JT, et al. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology 1998;115:1518–24.
[45] Yin HK, Wu HE, Li QX, et al. Pancreatic stenting reduces post-ERCP pancreatitis and biliary sepsis in high-risk patients: A randomized, controlled study. Gastroenterol Res Pract 2016;2016:9687052.
[46] Andrade-Dávila VF, Chávez-Tostado M, Dávalos-Cobián C, et al. Rectal indomethacin versus placebo to reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography: Results of a controlled clinical trial. BMC Gastroenterology 2015;15.
[47] Elmunzer BJ, Higgins PDR, Saini SD, et al. Does rectal indomethacin eliminate the need for prophylactic pancreatic stent placement in patients undergoing high-risk ercp post hoc efficacy and cost-benefit analyses using prospective clinical trial data. Am J Gastroenterol 2013;108:410–5.
[48] Khoshbaten M, Khorram H, Madad L, et al. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol 2008;23:e11–6.
[49] Murray B, Carter R, Imrie C, et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003;124:1786–91.