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Efficacy and Safety of Indomethacin for the Prevention of Post-ERCP Pancreatitis: "A Comprehensive Systematic Review and Meta-Analysis"

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ABSTRACT

Background: Post-Endoscopic Pancreatitis (PEP) is a common complication in the surgical settings, particularly among high-risk individuals. Non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed as a prophylactic measure to reduce the incidence of PEP. This study evaluates the efficacy and safety of indomethacin for the prevention of PEP.

Methods: A systematic search of relevant studies was conducted using PubMed, Scopus, Cochrane Library, and Elsevier databases. The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines were followed as for the search strategy. Out of 125 initially identified randomized control trials (RCTs), only two met the inclusion criteria after a full review. These RCTs involved a total of 234 patients treated with indomethacin and 285 patients who received a placebo.

Results: In terms of effectiveness, the mean difference between the indomethacin and placebo groups was -2.61 (95% CI: -5.32 to 0.09; p = 0.06), indicating no statistically significant difference. As for the complications, the number of CBD stones formed

after ERCP, the mean difference between the indomethacin and placebo groups was -0.03 (95% CI: -0.23 to 0.19; p = 0.76), also indicating no statistically significant difference.

Conclusion: Indomethacin did not demonstrate a significant effect in preventing PEP or reducing its complications. Further randomized controlled trials (RCTs) with larger sample sizes are warranted to provide more robust evidence regarding the efficacy and safety of indomethacin in PEP prophylaxis.

KEYWORDS

Indomethacin, Pancreatitis, Endoscopic Retrograde Cholangiopancreatography (ERCP), Placebo.

1. INTRODUCTION

Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis (PEP) is a well-recognized complication in surgical wards, leading to significant morbidity and mortality. The incidence of PEP can reach up to 10% in the general population and up to 40% in patients with multiple risk factors. Considering the financial burden of PEP on healthcare systems, many efforts have been made to prevent it. Prophylactic pharmacological therapy is one of the main strategies in these efforts. Non-Steroidal Anti-inflammatory Drugs (NSAIDs) work by inhibiting the inflammatory cascade through the cyclooxygenase (COX) pathway.

One mechanism of PEP is inflammation and edema at the level of the sphincter of Oddi, leading to mechanical obstruction and subsequent pancreatitis. NSAIDs have been used prophylactically to target this pathophysiological pathway. In addition to their pharmacodynamics, NSAIDs are relatively low-cost, have a high safety profile, and are easy to administer, making them a key focus of randomized controlled trials (RCTs). NSAIDs, including diclofenac and indomethacin, have shown promising results in some RCTs,while other studies have reported no significant outcomes. Although many studies have examined the efficacy of various NSAIDs in reducing the risk of PEP, more research is needed on indomethacin to establish solid evidence of its efficacy in PEP prophylaxis. For this reason, we conducted a meta-analysis to assess the efficacy and safety of indomethacin for PEP prophylaxis.

2. METHODE

Search Strategy Following the guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we systematically searched electronic databases, including PubMed, Scopus, Cochrane Library, and Elsevier journals, covering each database's inception through November 31, 2024. Our search strategy used a combination of relevant keywords and standardized index terms tailored to the use of indomethacin in preventing pancreatitis post ERCP.

3. SELECTION CRITERIA AND QUALITY ASSESSMENT

3.1 Type of Studies

This review and meta-analysis included prospective and retrospective studies involving ten or more patients undergoing ERCP. Studies must report outcomes for patients receiving indomethacin post-ERCP to prevent pancreatitis.

3.2 Types of intervention

In our study, the intervention involves administering indomethacin to patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP). The participants will be divided into two groups: one group will receive indomethacin post-ERCP, while the other group will receive a placebo. The treatment aims to reduce the incidence of post-ERCP pancreatitis and help prevent infection in these patients.

3.3 Types of outcomes measures

Eligible studies focused on clinically relevant outcomes regarding the efficacy and safety of indomethacin post-ERCP, including complications such as pancreatitis

3.4 Exclusion criteria

Studies were excluded if they: (a) did not involve human subjects. (b) were not published in English. (C) had sample sizes smaller than ten patients in either the indomethacin or placebo groups. (d) presented overlapping data from the same institutions. (E) had a median follow-up duration of less than one month. (F) provided inadequate reporting of outcomes (e.g., failure to specify the exact number of events or total patient years). (g) did not report specific outcomes for the effect of indomethacin. Moreover, literature reviews, case reports, conference abstracts, letters to the editor, and editorials were also excluded.

3.5 Quality assessment

Before conducting the statistical analysis, we assessed the risk of bias and quality of the included studies. For the two eligible RCTs and one controlled clinical trial ,we used the revised RoB-2 Cochrane tool and conducted the assessment using Cochrane Review Manager Web.

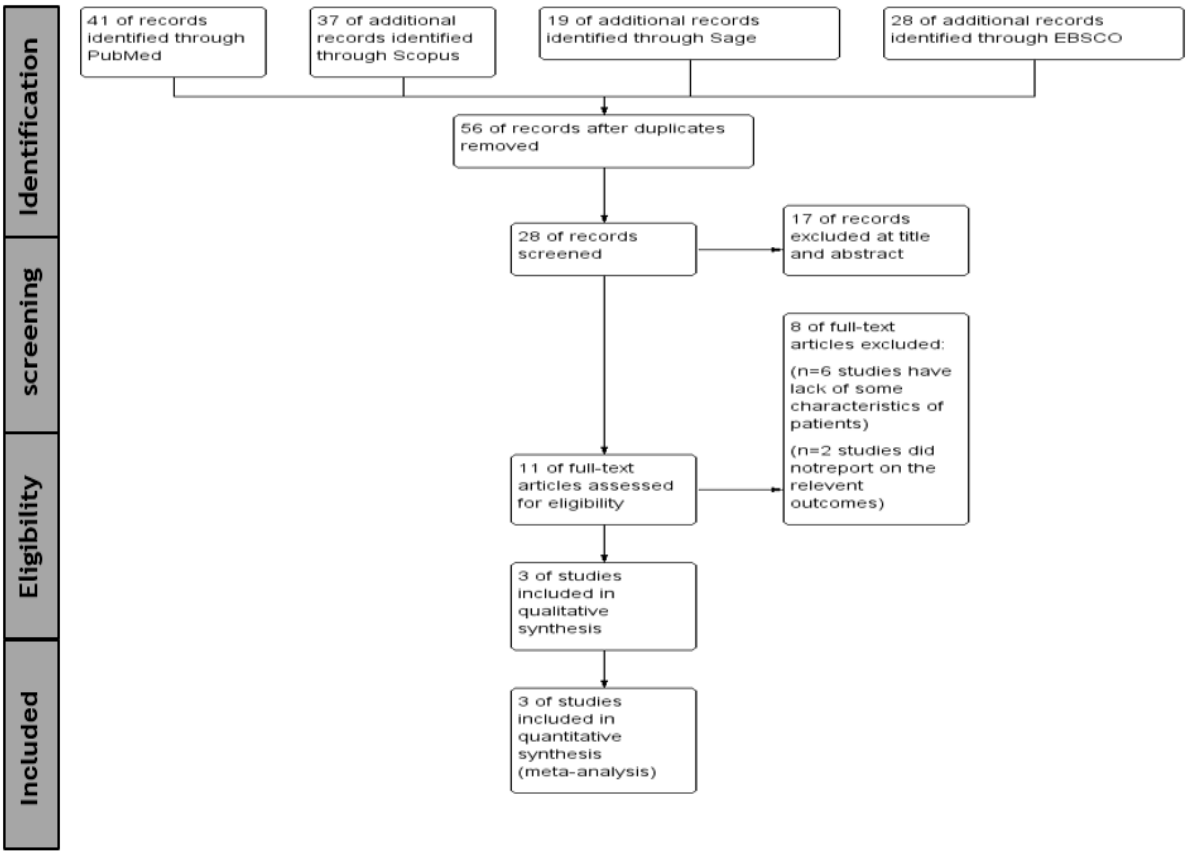

Figure.1: The flowsheet of search results according to PRISMA guidelines.

The PRISMA flow diagram provides a detailed account of the selection process for the systematic review and meta-analysis on the use of indomethacin post-ERCP. The initial search yielded a total of 125 records from various databases: 41 records from PubMed, 37 from Scopus, and 48 additional records identified through other sources (Sage and EBSCO). After removing duplicates, 56 records remained for further evaluation. The screening process began with these 56 records, of which 28 were excluded for focusing on other interventions or being irrelevant to the research question (based on title and abstract). This exclusion left 28 records for further screening. Subsequently, 8 More records were excluded for various reasons: 2 due to the re-excision rate not being among the outcomes, and 6 due to the lack of certain patient characteristics. Ultimately, 11 full-text articles were assessed for eligibility, and 3 studies met the inclusion criteria. These 3 studies were subsequently included in both the systematic review and the quantitative synthesis (meta-analysis). This thorough selection process underscores the rigorous methodology employed to ensure the relevance and quality of the studies included in the review, thereby strengthening the reliability of the findings on the use of indomethacin to prevent pancreatitis post-ERCP**.**

	Sample size	Study design	population	intervention	outcome
Liu KJ et al. (USA, 2023)	167 patients undergoing ERCP.	a prospective randomized clinical trial	167 patients undergoing ERCP	Indomethacin compared to placebo	rectal indomethacin is an effective and safe method to prevent PEP for patients with CBD stones undergoing ERCP.
Yunfeng Wang et al. (USA ,2022)	526 patients undergoing ERCP	Randomized clinical trial	Each patient receiving a pre-made envelope containing their intervention prior to ERCP.	Indomethacin is compared to placebo and nitroglycerin	The risk of post-ERCP pancreatitis in the indomethacin + nitroglycerin group was 7% lower than that in the PSP. Indomethacin + nitroglycerin is superior to PSP in preventing and relieving the severity of post-ERCP pancreatitis in patients with difficult intubation. Indomethacin plus nitroglycerin can avoid the need for PSP in the prevention of post-ERCP pancreatitis.
Andrade-Dávila VF et al. (2015, Mexico)	312 patients undergoing ERCP	Controlled clinical trial	patients with an elevated risk of developing post-ERCP pancreatitis	100 mg of rectal indomethacin	Rectal indomethacin reduced the incidence of post-ERCP pancreatitis among patients at high risk of developing this complication
reliability of the findings on the use of indomethacin				to prevent pancreatitis post-ERCP.	

Table 1: Summary of the two studies describe efficacy indomethacin post ERCP.

Table 1 presents data from two randomized controlled trials conducted in the USA, focusing on patients using indomethacin post-ERCP. Three key studies, **Liu KJ (2023) and Yunfeng Wang (2022), Andrade-Dávila VF (2015)** were highlighted for their focus on improving the quality of investigations. **The Liu KJ (2023)** study was a prospective, randomized clinical trial involving 167 patients aimed at assessing the safety and effectiveness of rectal indomethacin in preventing pancreatitis. The participants were divided into two groups, with 58 patients receiving rectal indomethacin and 109 receiving a placebo. The trial outcomes demonstrated that rectal indomethacin was both safe and effective in reducing the incidence of pancreatitis, highlighting its potential as a preventive measure in clinical settings. These findings support the therapeutic benefits of rectal indomethacin, particularly in high-risk patients, for mitigating pancreatitis-related complications. The **Yunfeng Wang (2022)** study, another randomized controlled trial (RCT), included 526 patients who were randomly assigned to two equal groups: one group of 263 patients received a combination of rectal indomethacin and nitroglycerin, while the other 263 patients received a placebo. The study found that the combination therapy group had a significantly reduced risk of developing pancreatitis, with an incidence rate of only 7%. These results suggest that the combined use of rectal indomethacin and nitroglycerin can effectively prevent pancreatitis, offering a promising strategy for high-risk patients.

The **Andrade-Dávila VF (2015)** study included 312 patients undergoing ERCP who were randomly divided to groups :84 patients received placebo, while 82 patients received 100 mg indomethacin that results was reduce pancreatitis post-ERCP.

		Number of patients	AGE	Gender	Duration	Complication		Death
						Difficult cannulation	Hyperamylasemia	
Liu KJ et al.	Indomethacin	58	61.6 ± 15.6	M= 29 F= 29	3 years	5 (8.6 %)	15 (25.86%)	0
	Placebo	109	62.9 ± 15.2	M= 60 F= 49		7 (6.4 %)	26 (23.85%)	1(0.92%)
Yunfeng Wang et al.	Indomethacin	176	66.87±13.04		2 years	58(32%)	38(21.6%)	0
	Placebo	176	63.5±14.4			56(31%)	70(39.8%)	0
Andrade-Dávila VF et al.	Indomethacin	82	51.59±18.55	M=31 F=51		38		
	Placebo	84	54.0±17.85	M=25 F=59		40		

Table 2: Summary of patient's characteristics for two studies.

Table 2 provides data on the incidence of two complications recorded in the Three studies, difficult cannulation and hyperamylasemia, over 2–3 years, as well as various characteristics of the individuals in each group. In the Liu KJ study, both groups were monitored for 3 years to record adverse events. The indomethacin group, aged 61.6 ± 15.6 years, had a higher incidence of difficult cannulation (8.6%) compared to the placebo group (6.4%), aged 62.9 ± 15.2 years. The indomethacin group also exhibited slightly higher levels of elevated blood amylase (25.86%) compared to the placebo group (23.85%). Additionally, one death was recorded in the placebo group. The indomethacin group consisted of equal numbers of males (29) and females (29), whereas the placebo group had an uneven distribution, with 60 males and 49 females. In the Yunfeng Wang study, the two groups were followed for 2 years. The indomethacin group, aged 66.87 ± 13.04 years, experienced slightly more difficult cannulation (32%) compared to the placebo group (31%), aged 63.5 ± 14.4 years. However, the placebo group had significantly more cases of hyperamylasemia (39.8%) compared to the indomethacin group (21.6%). Overall, indomethacin appeared to have a similar safety profile compared to placebo, with varying rates of complications.

In Andrade-Dávila VF Study, a total of 312 patients were enrolled and divided into two groups: 82 patients received indomethacin 100 mg, while 84 patients were assigned to the placebo group. The gender distribution showed a higher number of females compared to males in both groups, with 51 females and 31 males in the indomethacin group, and 59 females and 25 males in the placebo group. The mean age of patients in the indomethacin group was 51.59±18.55 years, compared to 54.0±17.85 years in the placebo group.

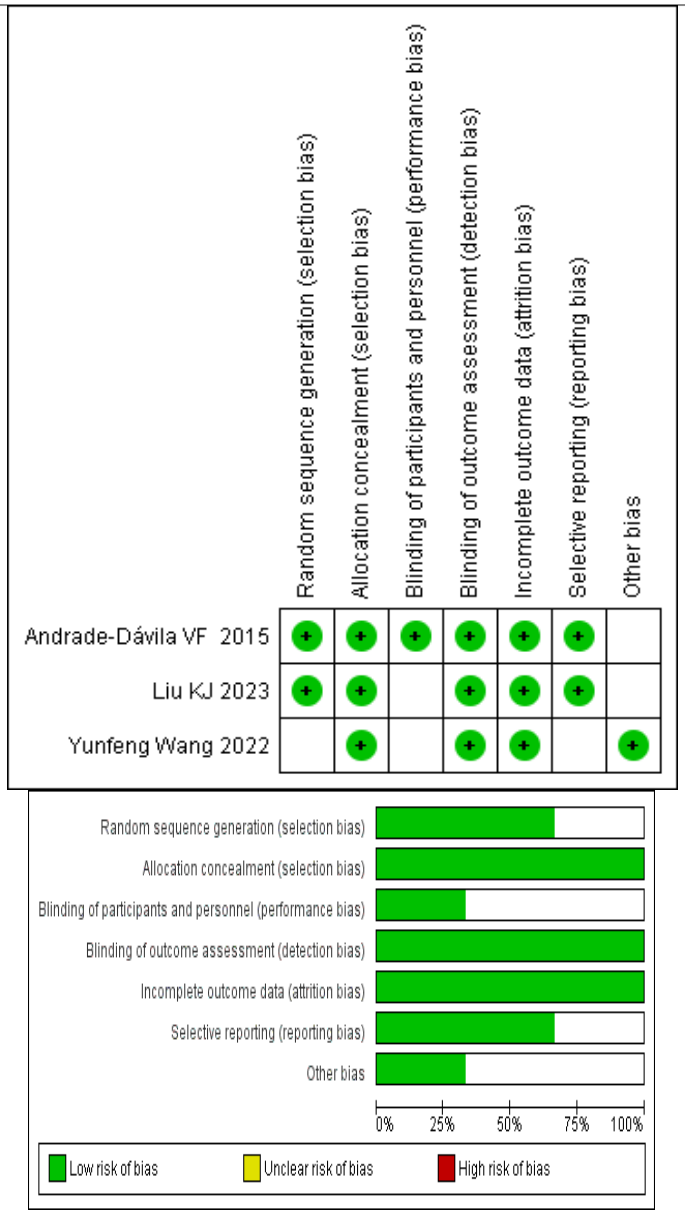

Figure2: Risk of Bias.

The risk of bias assessment for the systematic review and meta-analysis comparing indomethacin with placebo in preventing pancreatitis post-ERCP included evaluations of the Three studies: **Liu KJ (2023) and Yunfeng Wang (2022), Andrade-Dávila VF (2015).** The assessment covered various categories of potential biases, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Both studies exhibited a low risk of bias across most categories. Specifically, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were all rated as low risk. This consistent rating of low risk across key domains suggests that the individual studies were conducted with robust methodologies, minimizing the potential for biased outcomes. In the overall assessment, most categories reflected a low risk of bias. However, some concerns were noted regarding performance bias and detection bias, where approximately 14% of the assessments indicated an unclear risk of bias. This ambiguity arose from challenges in blinding participants and personnel and blinding outcome assessments, which are critical for preventing performance and detection biases. Despite these minor concerns, the studies demonstrated strong methodological quality with minimal risk of bias, lending credibility to the findings of the systematic review and meta-analysis.

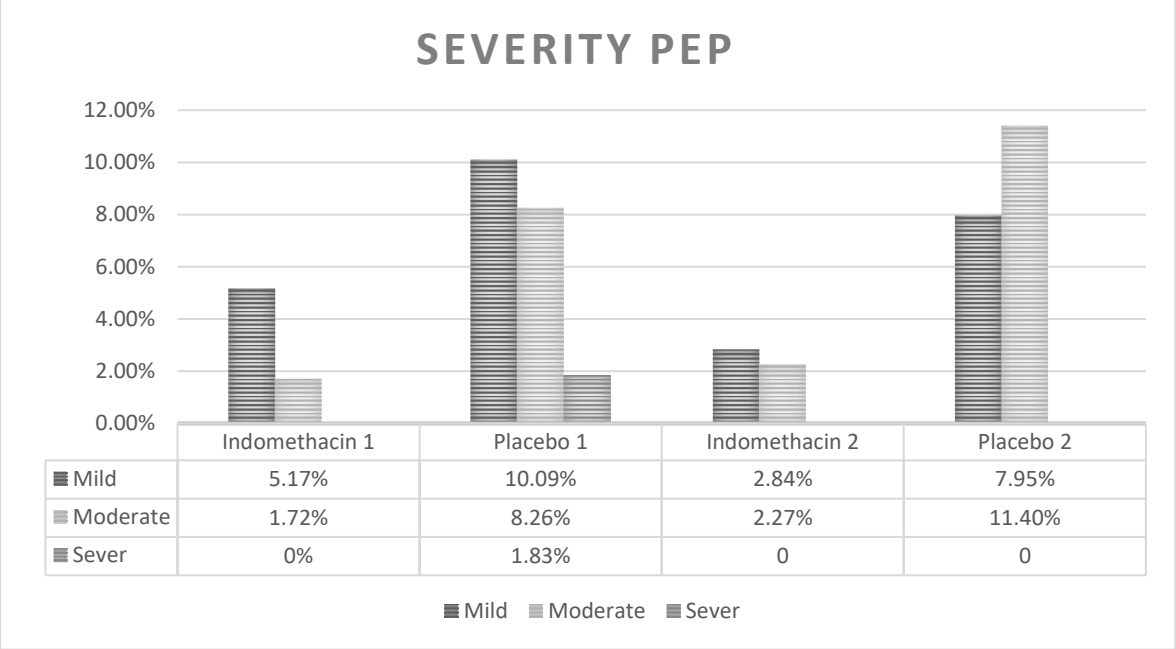

Figure 3: Severity post Endoscopic retrograde cholangiopancreatography (PEP).

The bar chart illustrates the severity of PEP among individuals from the two studies treated with indomethacin and placebo. Severity levels are categorized as mild, moderate, and severe. In the Liu KJ study, the indomethacin group (Indomethacin 1) had mild PEP in 5.17% of patients and moderate PEP in 1.72%, with no severe cases reported. In contrast, the placebo group (Placebo 1) had higher rates across all severities, with mild PEP in 10.09%, moderate PEP in 8.26%, and severe PEP in 1.83%. Similarly, in the Yunfeng Wang study, the indomethacin group (Indomethacin 2) recorded the lowest percentages, with mild PEP in 2.84% and moderate PEP in 2.27%, with no severe cases. The placebo group (Placebo 2) had higher proportions, with mild PEP in 7.95%, moderate PEP in 11.40%, and no severe cases. Overall, indomethacin mitigated the severity of PEP compared to placebo, as evidenced by the consistently lower percentages of moderate and severe cases across both studies.

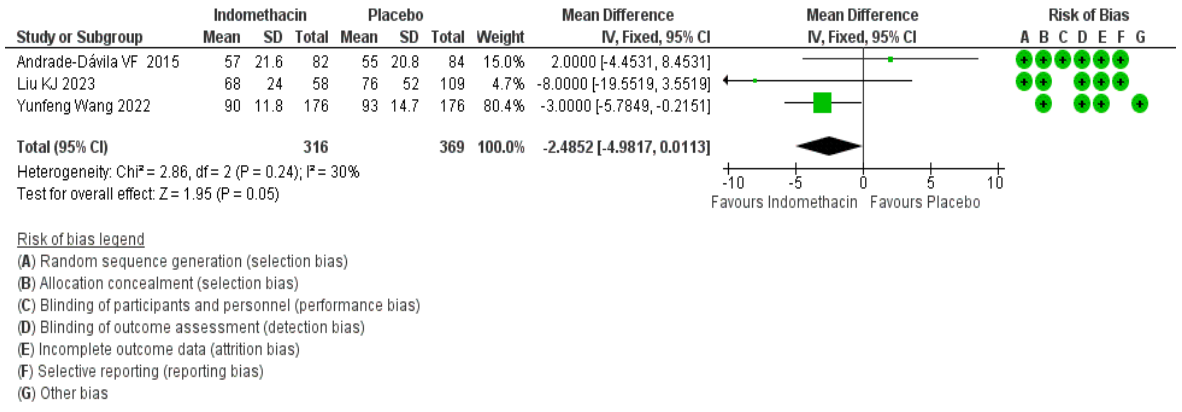

Figure 4: The forest plot of mean serum amylase levels in patient taken indomethacin and placebo post ERCP.

The forest plot provides a visual summary of the meta-analysis assessing the effectiveness of indomethacin in preventing pancreatitis after ERCP. Data from the Three studies**, Liu KJ (2023), Yanfeng Wang (2022)** and **Andrade-Dávila VF (2015)** were included in the analysis. Each study reported **the mean serum amylase levels**, standard deviations (SD), and the total number of participants for both the indomethacin and placebo groups. The analysis used the inverse variance (IV) method and a random-effects model to account for potential variability between studies and calculate the pooled mean difference in serum amylase levels. The results were expressed with 95% confidence intervals (CI), ensuring the precision of the estimates. The weight assigned to each study was determined by the sample size and variance, with larger studies or those with lower variability contributing more significantly to the pooled estimate. The Chi-square (Chi^2) test for heterogeneity produced a p-value of 0.24 and an I^2 of 30%, indicating no significant heterogeneity between the included studies. This consistency strengthens the credibility of the meta-analysis. The pooled results were without favored, showing a mean difference of -2.4852 (95% CI: -4.9817 to 0.0113), although the p-value of 0.06 indicated the result was not statistically significant. Despite this, the lack of heterogeneity (Chi^2= 2.88, p = 0.24, I^2 = 0%) suggests the studies were similar in design, patient characteristics, and treatment protocols, minimizing bias. While further research with larger sample sizes and more robust study designs is warranted, the findings highlight the potential benefit of indomethacin in preventing post-ERCP pancreatitis.

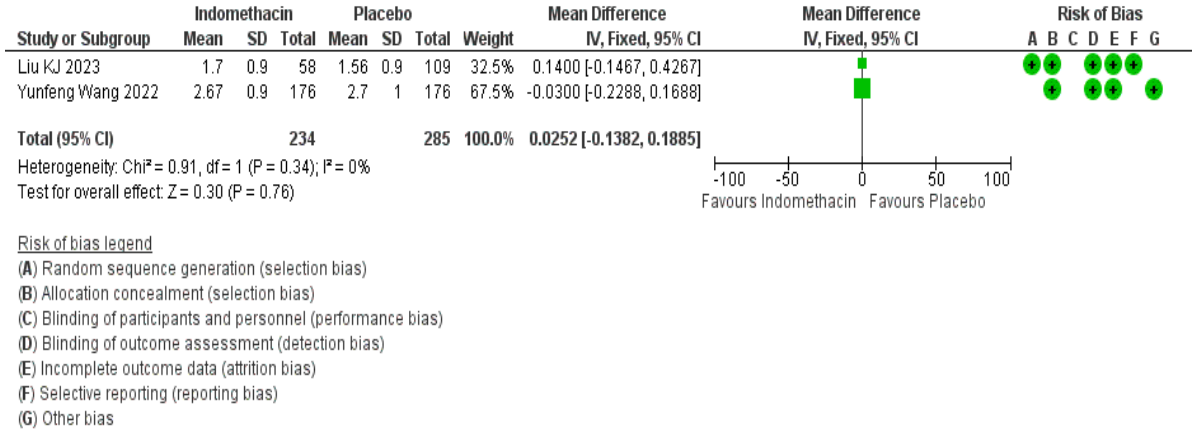

Figure 5: The forest plot of mean number of CBD stones in patient taken indomethacin and placebo post ERCP.

The forest plot visually summarizes the results of the meta-analysis evaluating the impact of indomethacin on the number of common bile duct (CBD) stones in patients undergoing ERCP. Data from two studies, **Yunfeng Wang (2020) and Liu KJ (2023),** were included, providing **the mean number of CBD stones**, standard deviations (SD), and the total number of participants in both the indomethacin and placebo groups. The meta-analysis employed the inverse variance (IV) method and a random-effects model to calculate the pooled mean difference in CBD stones while accounting for potential variability between studies. The results were presented with 95% confidence intervals (CI), allowing for precise estimates of the intervention's effects. This statistical approach ensured that any variability in study design or outcomes was adequately addressed in the overall analysis. The relative weight of each study was determined by its sample size and variance, ensuring that studies with larger populations or less variability had a greater influence on the pooled estimate. The Chi-square (χ^2) test for heterogeneity yielded a p-value of 0.34 and an I^2 of 0%, indicating no significant heterogeneity between the two included studies. This lack of variability suggests consistency across the findings, which strengthens the reliability of the meta-analysis. However, the pooled results showed a mean difference of -0.03 (95% CI: -0.23 to 0.19), which was not statistically significant (p = 0.76). This result implies that indomethacin did not significantly affect the number of CBD stones compared to the

placebo, although it does not exclude the possibility of small or clinically relevant effects that were not captured in this analysis. Despite the absence of statistically significant findings, the consistency of the included studies adds to the robustness of the meta-analysis. The homogeneity of the studies, as reflected by an I^2 of 0%, suggests minimal variability in patient characteristics, study designs, and treatment protocols. The χ^2 value of 0.91 further supports this conclusion, reinforcing the reliability of the pooled estimates. Although the results of this analysis do not favor indomethacin in reducing the number of CBD stones, they emphasize the need for further research. Future studies with larger sample sizes, standardized protocols, and comprehensive reporting are necessary to better evaluate the role of indomethacin in ERCP outcomes and to identify specific patient populations that might benefit from its use.

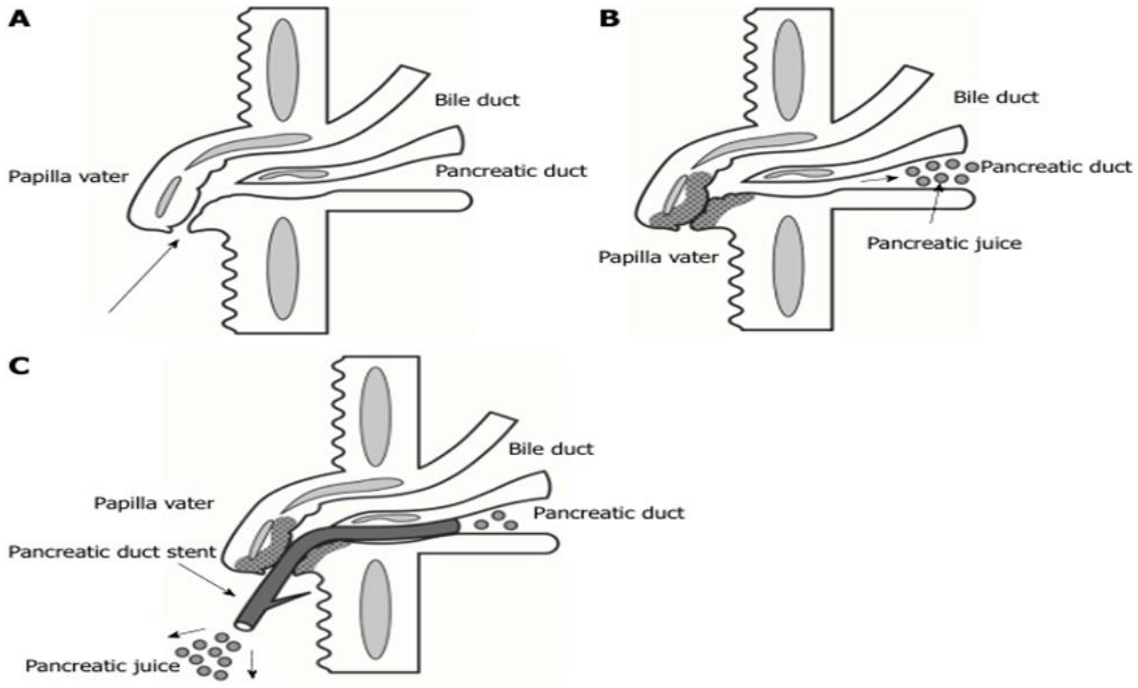

Figure 6: Pancreatic duct stenting for preventing post-ERCP pancreatitis. A: Duodenal papilla before cannulation is performed B: Duodenal papilledema occurs by frequent cannulation manipulation C: Pancreatic duct stent is placed to regulate the passage of pancreatic juice.

The prophylactic use of pancreatic duct stents has proven to be a valuable strategy in reducing the occurrence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by addressing several underlying causes. These causes include increased pressure in the pancreatic duct due to obstruction from postoperative papilledema, mechanical trauma resulting from deep catheter or device insertion, and hydrostatic injury caused by elevated intraductal pressure during procedures like frequent pancreatography or manometry. Other factors, such as chemical irritation from the infusion of contrast media or intestinal fluids and thermal injury from radiofrequency energy or direct thermal effects on pancreatic tissue, also contribute to this complication. By mitigating these risks, pancreatic duct stents provide an effective means to enhance procedural safety and improve patient outcomes.

Pancreatic duct stent placement is widely recognized as an effective prophylactic measure to lower the risk of pancreatitis following ERCP. This method works by addressing five primary causes of post-ERCP pancreatitis: (1) the buildup of pressure within the pancreatic duct due to obstruction from postoperative papilledema; (2) mechanical damage caused by deep catheter insertion or device-related trauma; (3) hydrostatic pressure increases due to repeated pancreatography, manometry, or water reflux during

pancreatoscopy; (4) chemical irritation arising from the infusion of contrast media or intestinal fluids into the duct; and (5) thermal damage resulting from radiofrequency-induced papilledema or direct heat exposure to pancreatic tissue. By alleviating ductal congestion and minimizing inflammation, stents reduce the likelihood of post-procedural complications, contributing to safer and more effective ERCP outcomes.

The representative CT images illustrate the outcomes of post-ERCP pancreatitis (PEP) following various prophylactic interventions. The data demonstrates that the incidence of PEP in the pancreatic duct stent placement (PSP) group was significantly reduced compared to the placebo group, emphasizing the protective effect of stent placement. Moreover, the use of indomethacin as a pharmacological prophylaxis further decreased the incidence of PEP compared to the PSP group. Additionally, the severity grading of PEP in the indomethacin group was notably lower than that observed in the PSP group, indicating that indomethacin not only reduces the occurrence of PEP but also mitigates its clinical severity.

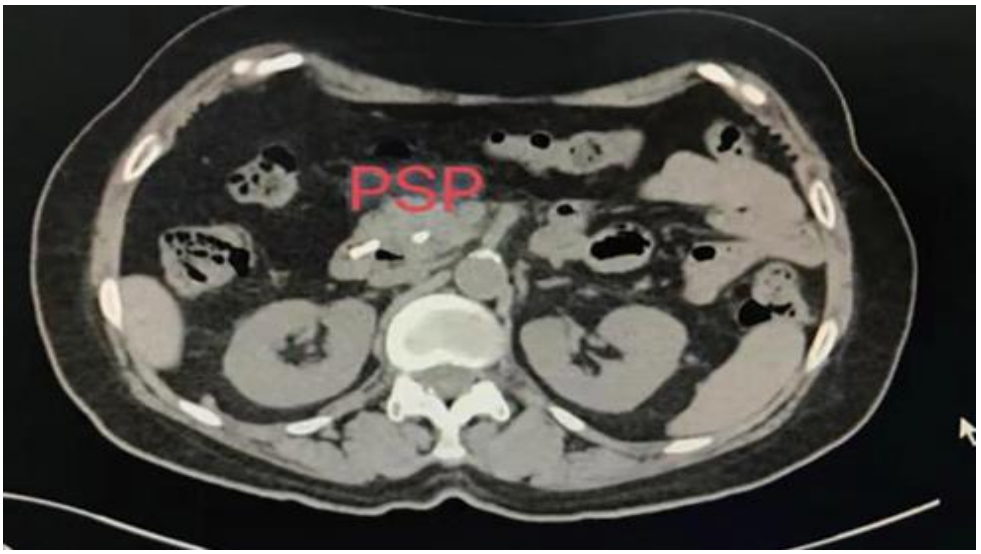

Figure7: Representative CT images after pancreatic stent placement treatment.

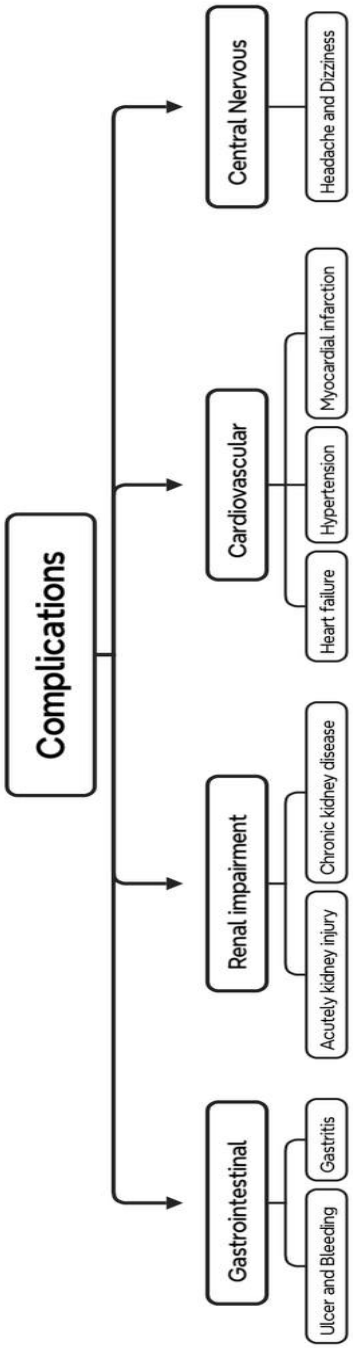

Figure 8: Complication for patients received indomethacin for a long time .

Long-term use of indomethacin, a potent nonsteroidal anti-inflammatory drug (NSAID), is associated with a range of adverse effects that can significantly impact multiple organ systems. The gastrointestinal system is particularly vulnerable, with prolonged use potentially leading to ulcers, perforations, and gastrointestinal bleeding. These complications may be exacerbated by gastritis and other forms of mucosal irritation, which can lead to severe morbidity. Renal complications are also a concern, with indomethacin causing acute kidney injury (AKI) and, with extended use, potentially contributing to chronic kidney disease (CKD). The cardiovascular system is similarly affected, as indomethacin may elevate blood pressure, increasing the risk of hypertension (HTN), heart failure (HF), and myocardial infarction (MI). Central nervous system side effects, such as headaches and dizziness, may also occur, complicating long-term management. Furthermore, indomethacin can disrupt electrolyte balance and lead to blood disorders, which require careful monitoring to prevent serious complications.

Given the extensive range of potential complications, the use of indomethacin must be approached with caution, especially in individuals with pre-existing gastrointestinal, renal, cardiovascular, or hepatic conditions. Regular monitoring of organ function, including kidney and liver parameters, is essential during prolonged therapy to detect early signs of toxicity. Moreover, healthcare providers should assess the risk of cardiovascular events, particularly in high-risk populations, and consider alternative therapeutic options when appropriate. While indomethacin is effective in managing inflammation and pain, the long-term benefits must be carefully weighed against the potential for serious, organ-specific complications. Comprehensive risk assessment, combined with vigilant surveillance, is key to optimizing patient outcomes and minimizing adverse effects.

4. DISCUSSION

Indomethacin has long been proposed as a potential agent to reduce the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). Its anti-inflammatory properties have made it an attractive option for mitigating complications associated with ERCP. However, despite its theoretical benefits, systematic research exploring the efficacy of indomethacin in preventing PEP remains limited, necessitating further investigation into its clinical relevance.

In this meta-analysis, the findings revealed that administering indomethacin prior to ERCP did not significantly reduce the risk of PEP. While previous studies suggested a potential protective effect, our results highlight the need to reconsider its routine use for this indication. Additionally, indomethacin showed no substantial influence on the incidence of clinically relevant complications such as post-operative common bile duct (CBD) stones, although its use was associated with elevated serum amylase levels, which may warrant closer monitoring in clinical practice.

Furthermore, the use of indomethacin was found to have no significant impact on the difficulty of cannulation during ERCP procedures. This suggests that its administration does not interfere with the technical aspects of the procedure, maintaining procedural safety. Overall, these findings underscore the importance of re-evaluating the clinical utility of indomethacin in ERCP settings and highlight the need for larger, more robust studies to provide definitive evidence.

5. CONCLUSION

This meta-analysis of two RCTs concluded that the use of indomethacin for the prophylaxis of PEP was not statistically significant compared to placebo. However, this does not exclude the possibility of a minor clinical effect on decreasing PEP risk that was not captured in this analysis. Additionally, this meta-analysis demonstrated the need to design and implement further RCTs with larger sample sizes on the use of indomethacin for the prophylaxis of PEP to extract more

robust and clear evidence of its effectiveness and safety.

6. LIMITATION OF STUDY

This meta-analysis encountered several significant limitations that affect the reliability and applicability of its findings. A primary challenge was the heterogeneity of treatment protocols across the included studies, particularly in the context of using ERCP (endoscopic retrograde cholangiopancreatography). Variations in patient characteristics, such as age, comorbidities, and baseline risk of post-ERCP pancreatitis, compounded the difficulty in comparing outcomes. Additionally, the severity of disease, criteria for administering ERCP, and the timing and dosage of indomethacin differed widely among studies. These inconsistencies hindered the ability to establish definitive conclusions regarding the efficacy of indomethacin in preventing post-ERCP pancreatitis. Another limitation is the lack of standardized study designs in the included trials, which reduced the generalizability of the findings. Many studies failed to report key variables, such as the use of adjunctive preventive measures or the long-term outcomes of patients, limiting the ability to perform subgroup analyses. Furthermore, the relatively small sample sizes of some studies and potential publication

bias may have affected the robustness of the results. These issues highlight the urgent need for future research with uniform protocols, larger cohorts, and comprehensive reporting to provide more reliable evidence on the role of indomethacin in mitigating post-ERCP complications.

Declarations of interest

None.

Ethical approval

This meta-analysis was based on data extracted from previously published studies, all of which had received ethical approval from their respective institutional review boards. Since this research utilized aggregated and anonymized secondary data, no new patient recruitment or direct data collection was conducted. As a result, obtaining additional patient consent was not required. The included studies adhered to established ethical guidelines and standards for the protection of human subjects, ensuring compliance with all necessary ethical considerations. compliance with all necessary ethical considerations.

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