

Systematic review and meta-analysis on the prophylactic role of non-steroidal anti-inflammatory drugs to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

AIM: To critically appraise the published randomized, controlled trials on the prophylactic effectiveness of the non-steroidal anti-inflammatory drugs (NSAIDs), in reducing the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

METHODS: A systematic literature search (MEDLINE, Embase and the Cochrane Library, from inception of the databases until May 2015) was conducted to identify randomized, clinical trials investigating the role of NSAIDs in reducing the risk of post-ERCP pancreatitis. Random effects model of the meta-analysis was carried out, and results were presented as odds ratios (OR) with corresponding 95%CI.

RESULTS: Thirteen randomized controlled trials on 3378 patients were included in the final meta-analysis. There were 1718 patients in the NSAIDs group and 1660 patients in non-NSAIDs group undergoing ERCP. The use of NSAIDs (through rectal route or intramuscular route) was associated with the reduced risk of post-ERCP pancreatitis [OR, 0.52 (0.38-0.72), $P = 0.0001$]. The use of pre-procedure NSAIDs was effective in reducing approximately 48% incidence of post-ERCP pancreatitis, number needed to treat were 16 with absolute risk reduction of 0.05. But the risk of post-ERCP pancreatitis was reduced by 55% if NSAIDs were administered after procedure. Similarly, diclofenac was more effective (55%) prophylactic agent compared to indomethacin (41%).

CONCLUSION: NSAIDs seem to have clinically proven advantage of reducing the risk of post-ERCP pancreatitis.

Key words: Non-steroidal drugs; Pancreatitis; Diclofenac; Indomethacin; Endoscopic retrograde cholangiopancreatography

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Core tip: Current meta-analysis of 13 randomized controlled trials on 3378 patients successfully demonstrates the usefulness of non-steroidal anti-inflammatory drugs (NSAIDs) in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Post-procedure use of NSAIDs by any route has clinically proven advantage of reducing 55% risk of post-ERCP pancreatitis. Diclofenac (55%) compared to indomethacin (41%) was more effective prophylactic agent.

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INTRODUCTION

Since its introduction into the field of gastroenterology, hepatology and hepato-pancreatico-biliary surgery, the endoscopic retrograde cholangiopancreatography (ERCP) has advanced to be an important and essential diagnostic and therapeutic tool. The introduction of magnetic resonance cholangiopancreatography and endoscopic ultrasound with several technological developments has sidelined ERCP into a largely a therapeutic tool in the management of sphincter of Oddi disorders, choledocholithiasis, pancreatic duct pathologies, and benign or malignant strictures of the common bile duct. However, ERCP carries significant risk, with post-ERCP pancreatitis being the most frequent

and dreaded of these. The reported prevalence of post-ERCP pancreatitis is as high as 10%^[1-4] in the medical literature. Nevertheless, it may exceed up to 30% in certain high-risk cluster of female patients with sphincter of Oddi dysfunction^[5]. Post-ERCP pancreatitis may result in prolonged hospital stay, pancreatic oedema, pancreatic necrosis, pancreatic pseudocyst, systemic inflammatory response syndrome and mortality up to 1% in addition to adding a significant financial burden on health-care resources^[6].

Considering the morbidity, mortality and financial burden related to post-ERCP pancreatitis, it is vital to consider every preventive strategy to reduce its incidence. Risk-benefit analysis and then right patient selection may be the best way to avoid un-necessary ERCP and its subsequent complications. Several studies have reported promising modalities of prophylaxis including pancreatic duct stenting of patients with sphincter of Oddi dysfunction, administration of NSAIDs of various types by various routes and other diverse measures. The evidence of these prophylactic measures is conflicting and so far has failed to demonstrate the accurate effectiveness^[7-11]. Based upon the available evidence, NSAIDs are the most commonly used modality for post-ERCP pancreatitis prevention. The possible advantages of NSAIDs use are cost-effectiveness, easily accessible and effortlessly administrable. The aim of this systematic review is to critically appraise the published randomized, controlled trials in the clinical effectiveness of the NSAIDs in reducing the risk of post-ERCP pancreatitis.

MATERIALS AND METHODS

Electronic medical databases such as the Medline, EMBASE, Cochrane Colorectal Cancer Group Controlled Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library and Science Citation Index Expanded were explored until May 2015 to find published randomized, controlled trials. The MeSH terms related to the NSAIDs and post-ERCP pancreatitis were retrieved from the search engine of PubMed and were used to search electronic databases. Attempts to include additional studies were also made by the hand searching of the citations of published studies. The statistical analysis of the extracted data was conducted according to the guidelines provided by the Cochrane Collaboration including the use of RevMan 5.3[®] statistical software, random-effects model analysis, heterogeneity testing by χ^2 test, heterogeneity quantification by I -squared test and the use of forest plots for the graphical display of the combined outcomes^[12-18]. The critical appraisal tool to score the quality of included trials was adopted from the published guidelines of Jadad *et al*^[19] and Chalmers *et al*^[20]. The short summary of the resulting evidence was presented in a tabulated form by using tool GradePro[®]^[21], provided by the Cochrane Collaboration.

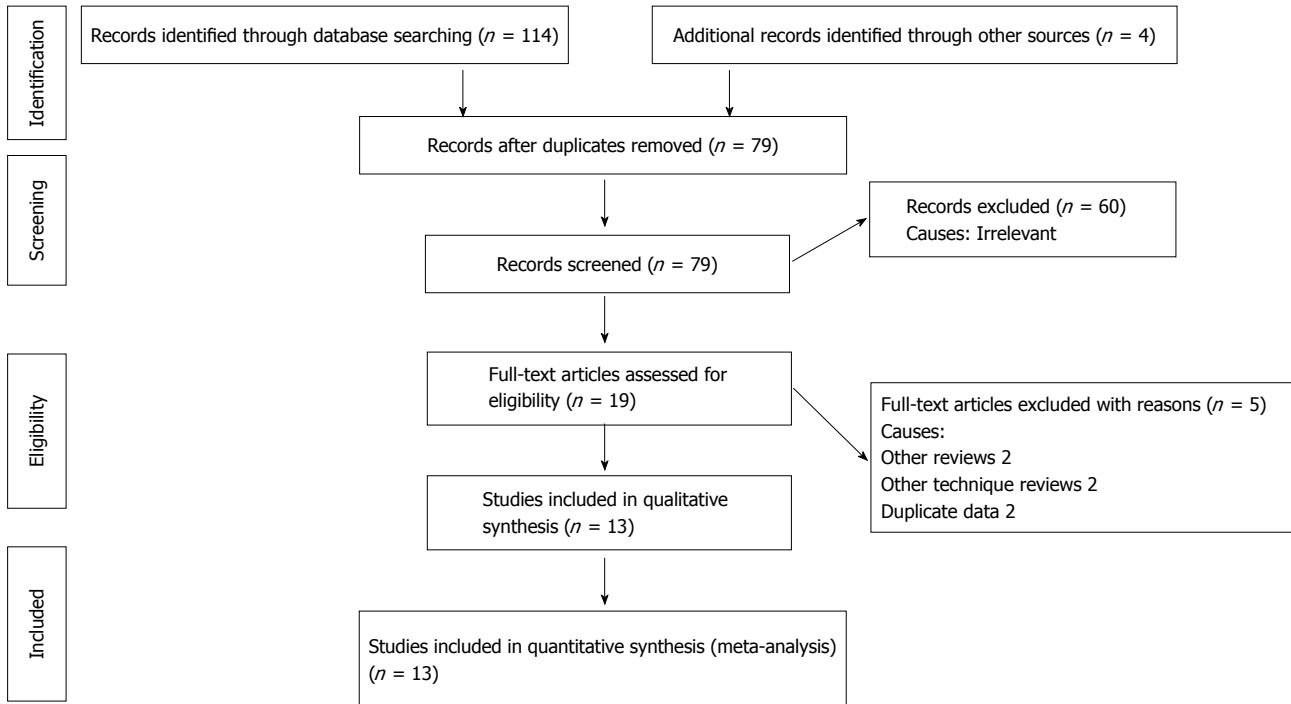


Figure 1 PRISMA flow chart.

RESULTS

Number of studies on first hit in search engines and their subsequent shortlisting is given in the PRISMA flow chart (Figure 1). Thirteen randomized, controlled trials^[22-34] on 3378 patients undergoing ERCP were analysed in this study. Some 1718 patients were assigned in NSAIDs group whereas 1660 patients were in no-NSAIDs group. The characteristics of included studies are given in Table 1. The short summary on the quality of evidence generated from the combined analysis of trials used in this meta-analysis is given in Table 2. The study quality based scores of included trials were graded adequate based upon the reporting of four quality indicator variables, *i.e.*, optimum randomization technique, power calculations, concealment and intention-to-treat analysis.

Incidence of post-ERCP pancreatitis in NSAIDs vs placebo trials

As shown in Figure 2A, there was minimal and non-significant heterogeneity [$\text{Tau}^2 = 0.11$, $\chi^2 = 18.60$, $\text{df} = 12$, ($P = 0.10$); $I^2 = 35\%$] among trials. In the random effects model (OR, 0.52; 95%CI: 0.38, 0.72; $Z = 4.02$; $P < 0.0001$) analysis, the risk of post-ERCP pancreatitis was significantly lower (48% lower) following the use of NSAIDs. The NNT was 16 with absolute risk reduction of 0.05.

Incidence of post-ERCP pancreatitis in per rectal NSAIDs vs placebo trials

As shown in Figure 2B, there was no heterogeneity [$\text{Tau}^2 = 0.11$, $\chi^2 = 9.86$, $\text{df} = 7$, ($P = 0.20$); $I^2 = 29\%$] among trials. In the random effects model (OR, 0.43;

95%CI: 0.28, 0.67; $Z = 3.77$; $P = 0.0002$) analysis, the risk of post-ERCP pancreatitis was significantly lower (57% lower) following rectal administration of NSAIDs.

Incidence of post-ERCP pancreatitis in diclofenac vs placebo trials

As shown in Figure 2C, there was significant heterogeneity [$\text{Tau}^2 = 0.38$, $\chi^2 = 14.49$, $\text{df} = 6$, ($P = 0.02$); $I^2 = 59\%$] among trials. In the random effects model (OR, 0.45; 95%CI: 0.24, 0.83; $Z = 2.55$; $P = 0.01$) analysis, the risk of post-ERCP pancreatitis was significantly lower (55% lower) following the use of diclofenac.

Incidence of post-ERCP pancreatitis in indomethacin vs placebo trials

As shown in Figure 2D, there was no heterogeneity [$\text{Tau}^2 = 0.00$, $\chi^2 = 3.81$, $\text{df} = 4$, ($P = 0.43$); $I^2 = 0\%$] among trials. In the random effects model (OR, 0.59; 95%CI: 0.39, 0.88; $Z = 2.61$; $P = 0.009$) analysis, the risk of post-ERCP pancreatitis was significantly lower (41% lower) following the use of indomethacin. Based upon this finding it seems like diclofenac is more effective NSAIDs compared to indomethacin for the prevention of post-ERCP pancreatitis.

Incidence of post-ERCP pancreatitis if NSAIDs are administered before procedure

As shown in Figure 2E, there was no heterogeneity [$\text{Tau}^2 = 0.05$, $\chi^2 = 5.96$, $\text{df} = 5$, ($P = 0.31$); $I^2 = 16\%$] among trials. In the random effects model (OR, 0.52; 95%CI: 0.34, 0.80; $Z = 2.93$; $P = 0.003$) analysis, the risk of post-ERCP pancreatitis was significantly lower (48% lower) if NSAIDs are administered before the

Table 1 Characteristics of included trials

Ref.	Year	Country	Time of administration	Route	Dose	Type of NSAIDs used
Cheon <i>et al</i> ^[22]	2007	United States	Before ERCP	Oral	50 mg	Diclofenac
Döbrönte <i>et al</i> ^[23]	2012	Hungary	Before ERCP	Rectal	100 mg	Indomethacin
Döbrönte <i>et al</i> ^[24]	2014	Hungary	Before ERCP	Rectal	100 mg	Indomethacin
Elmunzer <i>et al</i> ^[25]	2012	United States	After ERCP	Rectal	100 mg	Indomethacin
Khoshbaten <i>et al</i> ^[26]	2008	Iran	After ERCP	Rectal	100 mg	Diclofenac
Montaño Loza <i>et al</i> ^[27]	2006	Mexico	Before ERCP	Rectal	100 mg	Indomethacin
Montaño Loza <i>et al</i> ^[28]	2007	Mexico	Before ERCP	Rectal	100 mg	Indomethacin
Murray <i>et al</i> ^[29]	2003	United Kingdom	After ERCP	Rectal	100 mg	Diclofenac
Otsuka <i>et al</i> ^[30]	2012	Japan	Before ERCP	Rectal	50 mg	Diclofenac
Park <i>et al</i> ^[31]	2014	United States	After ERCP	Intramuscular	90 mg	Diclofenac
		South Korea				
Senol <i>et al</i> ^[32]	2009	Turkey	After ERCP	Intravenous infusion	75 mg	Diclofenac
Sotoudehmanesh <i>et al</i> ^[33]	2007	Iran	Before ERCP	Rectal	100 mg	Indomethacin
Zhao <i>et al</i> ^[34]	2014	China	After ERCP	Intramuscular	75 mg	Diclofenac

NSAIDs: Non-steroidal anti-inflammatory drugs; ERCP: Endoscopic retrograde cholangio-pancreaticography.

Table 2 Summary and strength of the evidence from trials analysed on GradePro®

Author(s): Sajid <i>et al</i>												
Date: 20/10/2015												
Question: NSAID's are an effective modality to reduce the incidence of post-ERCP pancreatitis?												
Settings: All patients undergoing booth elective or emergency ERCP in endoscopy department for any indication by an experienced gastroenterologist/endoscopists												
Bibliography: Adapted from the Cochrane Database of Systematic Reviews [2015, Issue (Is)]												
Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID's vs placebo	Control	Relative (95%CI)	Absolute		
Incidence of overall pancreatitis (follow-up mean 3 mo; assessed with: Odds ratio)												
14	Randomised trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association	138/1900 (7.3%)	248/1878 (13.2%)	OR 0.49 (0.36 to 0.67)	63 fewer per 1000 (from 40 fewer to 80 fewer)	High	Critical
								15.7%		73 fewer per 1000 (from 46 fewer to 94 fewer)		

NSAIDs: Non-steroidal anti-inflammatory drugs; ERCP: Endoscopic retrograde cholangio-pancreaticography.

procedure of ERCP compared to placebo.

Incidence of post-ERCP pancreatitis if NSAIDs are administered after procedure

As shown in Figure 2F, there was minimal heterogeneity [$\tau^2 = 0.21$, $\chi^2 = 10.30$, $df = 5$, ($P = 0.07$); $I^2 = 51\%$] among trials. In the random effects model (OR, 0.45; 95%CI: 0.27, 0.77; $Z = 2.90$; $P = 0.004$) analysis, the risk of post-ERCP pancreatitis was significantly lower (55% lower) if NSAIDs are administered after the procedure of ERCP compared to placebo.

DISCUSSION

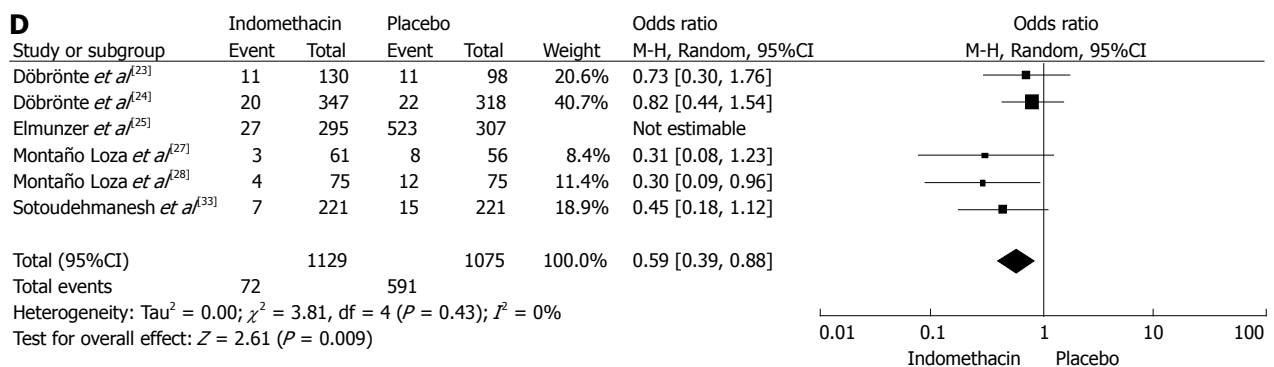
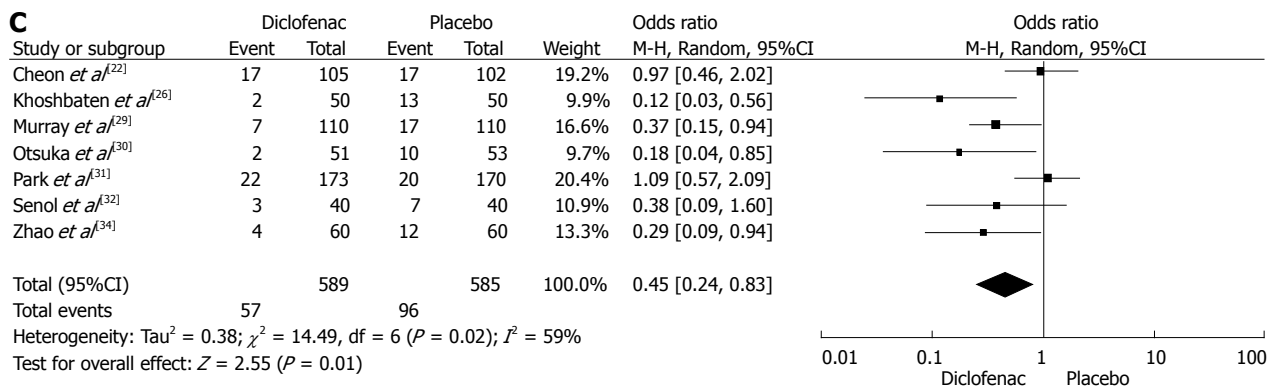
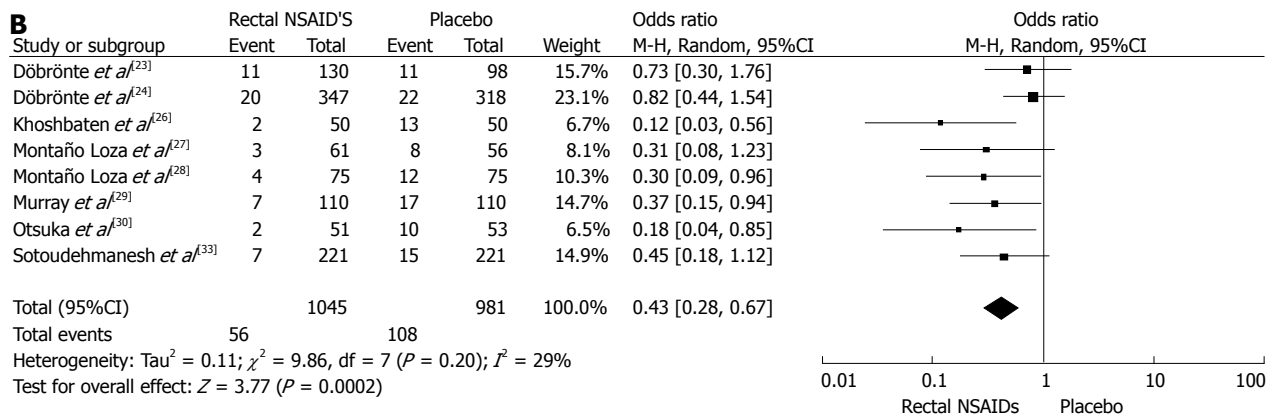
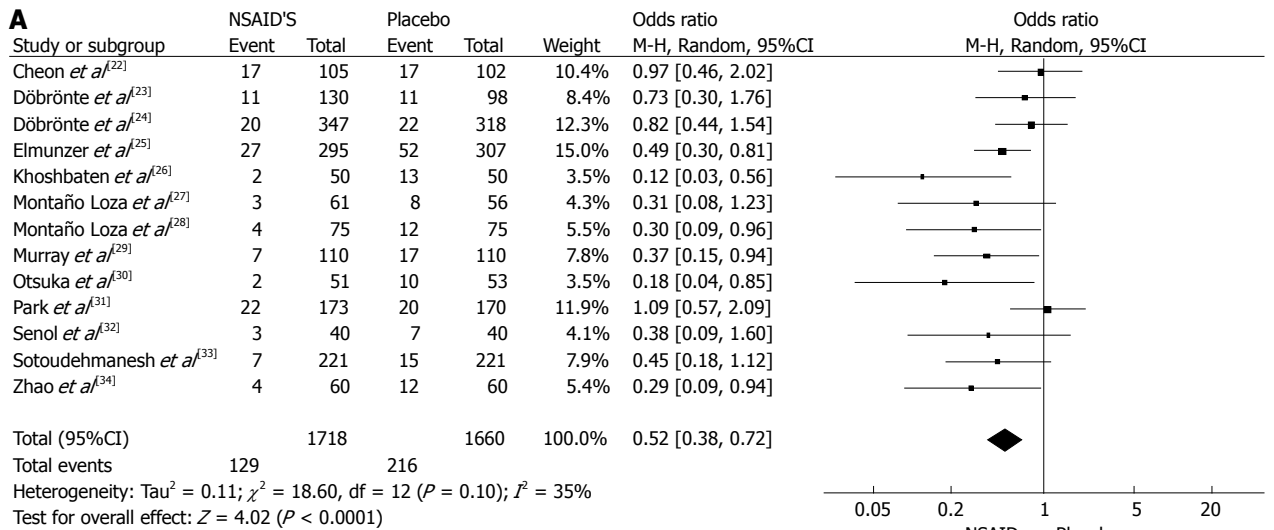
Summary of main results

Results of this meta-analysis demonstrate that the use

of NSAIDs (by any route of administration) meaningfully reduces the incidence of post-ERCP pancreatitis; rectal administration is slightly more effective; diclofenac seems to be clinically better than indomethacin and post-ERCP administration has shown superior results. The use of pre-procedure NSAIDs was effective in reducing approximately 48% but the risk of post-ERCP pancreatitis was reduced by 55% if NSAIDs were administered after the procedure.

Overall completeness and applicability of evidence

The findings of current study are pertinent to only those groups of patients which may require either therapeutic or diagnostic ERCP and fit enough to undergo the procedure. Despite the reporting of several systematic reviews and meta-analysis^[35-46] evaluating the role of NSAIDs in reducing



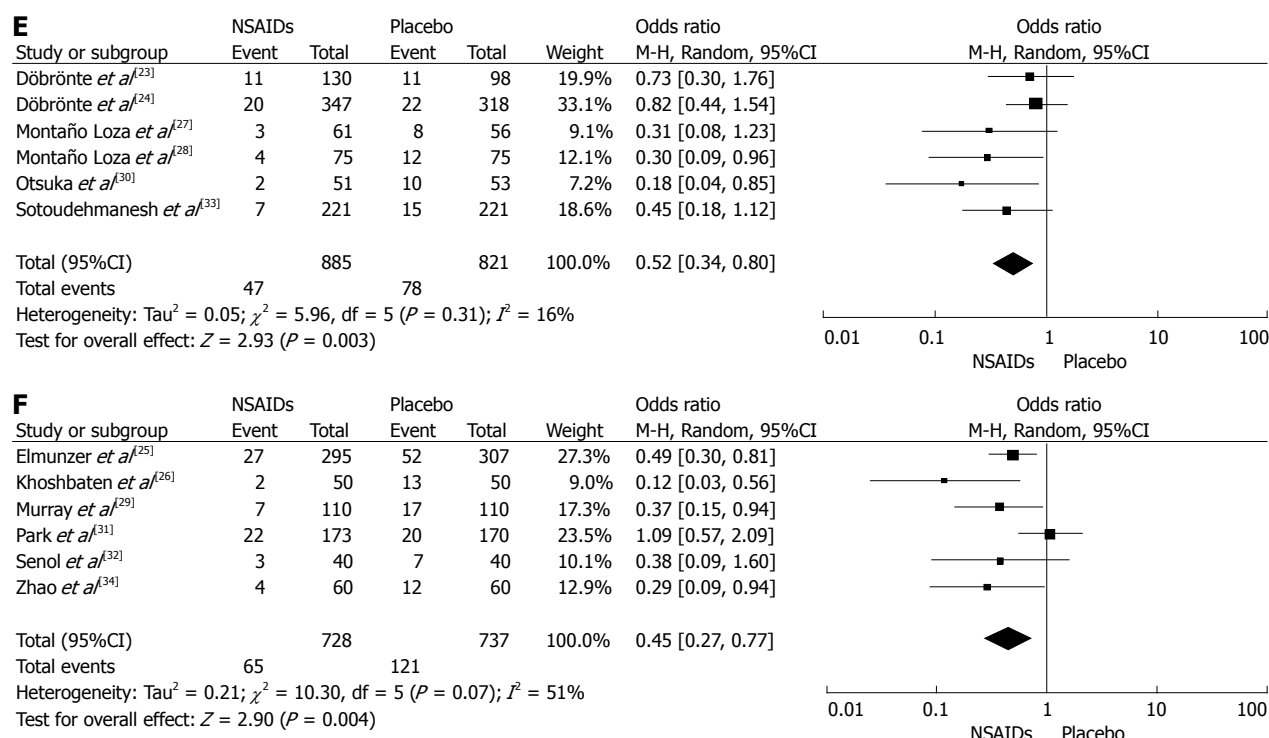


Figure 2 Forest plot for incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. A: In non-steroidal anti-inflammatory drugs vs placebo groups; B: In rectal non-steroidal anti-inflammatory drugs vs placebo groups; C: In diclofenac vs placebo groups; D: In indomethacin vs placebo groups; E: In pre-endoscopic retrograde cholangiopancreatography non-steroidal anti-inflammatory drugs vs placebo groups; F: In post-endoscopic retrograde cholangiopancreatography non-steroidal anti-inflammatory drugs vs placebo groups. Odds ratios are shown with 95% CIs.

the risk of consequent pancreatitis resulting from ERCP, this is the only study providing evidence on the role of NSAIDs, route of NSAIDs administration, type of NSAIDs being more effective and the timing of the NSAIDs administration to reduce the incidence of post-ERCP pancreatitis.

Quality of evidence

This study reports a total of 3378 participants from 13 randomized, controlled trials undergoing ERCP reporting post-ERCP pancreatitis as primary outcome preferentially. The risk of bias in the included trials was low to moderate when scores against the standard quality guidelines and therefore, the quality of resulting evidence may be considered adequate (Table 2). The variable experience of endoscopists might have influenced the outcomes. Other confounding factors which might have influenced the final outcome of the ERCP include the use of different endoscopes, type and dosage of sedation, variable use of scope-guide technique, indications of ERCP, sundry patient selection and diverse biochemical measuring tools for the diagnosis of post-ERCP pancreatitis.

Potential biases in the review process

Authors adopted the standard Cochrane Collaboration methodology to perform the statistical analysis, interpretation as well as to present the quality of evidence. The quality of included (Table 3) randomized, controlled trials was assessed for risk of bias in one of the six domains (blinding) and at unclear risk of bias in another domain (allocation concealment). The low risk of bias

was mainly attributable to the presence of blinding in all the trials and presence of allocation concealment in the majority of the studies. Presence of adequate randomization technique and optimum utilization of the power calculations in all included trials provided adequate strength to generate higher level of evidence to support the conclusion. There are no trials comparing pre-procedure vs post-procedure prophylactic use of NSAIDs. This inference was made based upon their comparisons against placebo. Same limitation also applies on the effectiveness of diclofenac vs indomethacin. However, the conclusion in terms of an individual agent vs other agent effectiveness and timing of NSAIDs administration may reluctantly be drawn from the available studies comparing effectiveness against placebo.

Agreement and disagreement with other published evidence

The findings of current meta-analysis are in accordance with the conclusions of the previously published reviews^[35-46]. However, this study provides up to date, comprehensive and cumulative evidence on the use of NSAIDs (by any route of administration) meaningfully reducing the incidence of post-ERCP pancreatitis, suggesting the rectal administration of NSAIDs being more effective, indomethacin proven to be clinically better than diclofenac and pre-ERCP administration of NSAIDs showing superior results.

Implications for practice and research

This study quite successfully validates that NSAIDs may

Table 3 Reported quality variables in included studies

Ref.	Randomization	Power calculations	ITT	Blinding	Concealment
Cheon <i>et al</i> ^[22]	Yes	Yes	Yes	Yes	Yes
Döbrönte <i>et al</i> ^[23]	Yes	Yes	No	Yes	Yes
Döbrönte <i>et al</i> ^[24]	Yes	Yes	No	Yes	Yes
Elmunzer <i>et al</i> ^[25]	Yes	Yes	Yes	Yes	Yes
Khoshbaten <i>et al</i> ^[26]	Yes	Yes	No	Yes	Yes
Montaño Loza <i>et al</i> ^[27]	Yes	Yes	No	Yes	Yes
Montaño Loza <i>et al</i> ^[28]	Yes	Yes	No	Yes	Not reported
Murray <i>et al</i> ^[29]	Yes	Yes	No	Yes	Yes
Otsuka <i>et al</i> ^[30]	Yes	Yes	No	Yes	Yes
Park <i>et al</i> ^[31]	Yes	Yes	No	Yes	Yes
Senol <i>et al</i> ^[32]	Yes	Yes	No	Not reported	Not reported
Sotoudehmanesh <i>et al</i> ^[33]	Yes	Yes	No	Yes	Yes
Zhao <i>et al</i> ^[34]	Yes	Yes	No	No	Not reported

routinely be used to prevent the post-ERCP pancreatitis. However, the aforementioned confounding factors influencing the final outcomes must be acknowledged and attempts must be made to generate less biased evidence by removing these limitations. This study categorically reports the superiority of rectal administration of NSAIDs, diclofenac over indomethacin and post-ERCP administration of NSAIDs to reduce post-ERCP pancreatitis. However, these results cannot be generalized because the preventative strategy for post-ERCP pancreatitis in group of patients with known peptic ulcer disease, asthma, and allergy to NSAIDs needs also to be formulated. In addition, NSAIDs cannot be used in patients with chronic kidney disease. Other measures to prevent post-ERCP pancreatitis must not be completely abandoned and may be applicable in these situations. In addition, there are no reported trials comparing pre-procedure vs post-procedure prophylactic use of NSAIDs. This inference was made based upon their comparisons against placebo. Same limitation also applies on the effectiveness of diclofenac vs indomethacin. Trials targeting these questions must be considered for a validated conclusion from direct evidence instead of the presented indirect inference. Current review is unable to quantify the potential complication of bleeding following the prophylactic use of NSAIDs in ERCP patients, especially in patients undergoing sphincterotomy simultaneously. Although this is beyond the scope of this study but reported incidence of bleeding is almost negligible. Neither the length of incision nor the pre-procedure use of aspirin or other NSAIDs appear to be important predictors of ERCP-sphincterotomy linked bleeding^[47].

COMMENTS

Background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis can be a serious complication resulting in increased mortality and morbidity in already sick patients. Therefore, the preventative strategies for post-ERCP are vital to reduce its consequences. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is simple, economical and reported to be effective to reduce the incidence of post-ERCP pancreatitis. This article highlights the evidence in the form of meta-analysis to define the role of NSAIDs.

Research frontiers

Other preventive measures to reduce the incidence of post-ERCP pancreatitis include sphincterotomy of the sphincter of Oddi and pancreatic duct stenting. However, the use of NSAIDs seems to be less invasive and most economical. Several studies have reported its effectiveness and current study is an attempt to advance this evidence further.

Innovations and breakthroughs

Current meta-analysis of 13 randomized controlled trials on 3378 patients successfully demonstrates the usefulness of NSAIDs in the prevention of post-ERCP pancreatitis. Post-procedure use of NSAIDs by any route has clinically proven advantage of reducing 55% risk of post-ERCP pancreatitis. Diclofenac (55%) compared to indomethacin (41%) was more effective prophylactic agent.

Applications

Based upon the findings of this study the use of NSAIDs has clinical advantage in the reduction of post-ERCP pancreatitis and may routinely be used.

Terminology

ERCP: Endoscopic retrograde cholangiopancreatography; NSAIDs: Non-steroidal anti-inflammatory drugs; MRCP: Magnetic resonance cholangiopancreatography.

Peer-review

The manuscript is overall well written.

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