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

Muhammad S Sajid, Amir H Khawaja, Mazin Sayegh, Krishna K Singh, Zinu Philipose

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.

Conflict-of-interest statement: None to declare.

Data sharing statement: We confirm that all authors were involved with the data extraction, data related conflict resolution by mutual consensus and data securing. This data is the sole property of the listed authors and we did not share this data with any other research team and we did not duplicate this data in any other article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Muhammad S Sajid, Surgical Associate Specialist, Department of General, Endoscopic and Laparoscopic Colorectal Surgery, Western Sussex Hospitals NHS Foundation Trust Worthing Hospital Worthing, Lyndhurst Road, Washington Suite, North Wing, Worthing, BN11 2DH, Worthing, West Sussex BN11 2DH, United Kingdom. surgeon1wrh@hotmail.com Telephone: +44-1903-205111-84760 Fax: +44-1903-285010

Received: June 9, 2015 Peer-review started: June 11, 2015 First decision: August 5, 2015 Revised: October 13, 2015 Accepted: November 10, 2015 Article in press: November 11, 2015 Published online: December 25, 2015

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.
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

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Sajid MS, Khawaja AH, Sayegh M, Singh KK, Philippe Z. Systematic review and meta-analysis on the prophylactic role of non-steroidal anti-inflammatory drugs to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis. World J Gastrointest Endosc 2015; 7(19): 1341-1349. Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i19/1341.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i19.1341

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 sideline ERCP into a largely a therapeutic tool in the management of sphincter of Oddi disorders, cholelithiasis, 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 unnecessary 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 $\chi^2$ 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.
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 diclofenac vs placebo trials
As shown in Figure 2C, there was significant heterogeneity \(\text{Tau}^2 = 0.38, \chi^2 = 3.81, \text{df} = 4, (P = 0.43); I^2 = 41\%\) 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 \(\text{Tau}^2 = 0.00, \chi^2 = 5.96, \text{df} = 5, (P = 0.31); I^2 = 16\%\) among trials. In the random effects model (OR, 0.59; 95%CI: 0.34, 0.80; \(Z = 2.93, P = 0.003\)) analysis, the risk of post-ERCP pancreatitis was significantly lower (41% lower) following the use of indomethacin.

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

**Table 1 Characteristics of included trials**

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

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

| Author(s): Sajid et al | Date: 20/10/2015 | Question: NSAID’s are an effective modality to reduce the incidence of post-ERCP pancreatitis? | Settings: All patients undergoing both 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)] |
|------------------------|------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| No. of studies         | Design           | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | NSAID’s vs placebo | Control | Relative (95%CI) | Absolute |
| 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) | 15.7% | 73 fewer per 1000 (from 46 fewer to 94 fewer) | High | Critical |

**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.

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

As shown in Figure 2F, there was minimal heterogeneity ($\tau^2 = 0.21, I^2 = 10.30, df = 5, (P = 0.07); I^2 = 51\%$) 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.

**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
### A

| Study or subgroup | NSAID's | Placebo |
|------------------|---------|---------|
|                  | Event   | Total   | Event | Total | Weight | Odds ratio M-H, Random, 95%CI |
| Cheon et al. [26] | 17      | 105     | 17    | 102   | 10.4%  | 0.97 [0.46, 2.02] |
| Doıbrönte et al. [23] | 11      | 130     | 11    | 98    | 8.4%   | 0.73 [0.30, 1.76] |
| Doıbrönte et al. [24] | 20      | 347     | 22    | 318   | 12.3%  | 0.82 [0.44, 1.54] |
| Elimunzer et al. [24] | 27      | 295     | 52    | 307   | 15.0%  | 0.49 [0.30, 0.81] |
| Khoshsbaten et al. [32] | 2       | 50      | 13    | 50    | 3.5%   | 0.12 [0.03, 0.56] |
| Montaño Loza et al. [20] | 3       | 61      | 8     | 56    | 4.3%   | 0.31 [0.08, 1.23] |
| Montaño Loza et al. [20] | 4       | 75      | 12    | 75    | 5.5%   | 0.30 [0.09, 0.96] |
| Murray et al. [28] | 7       | 110     | 17    | 110   | 7.8%   | 0.37 [0.15, 0.94] |
| Otsuka et al. [20] | 2       | 51      | 10    | 53    | 3.5%   | 0.18 [0.04, 0.85] |
| Park et al. [28] | 22      | 173     | 20    | 170   | 11.9%  | 1.09 [0.57, 2.09] |
| Senol et al. [20] | 3       | 40      | 7     | 40    | 4.1%   | 0.38 [0.09, 1.60] |
| Sotoudehmanesh et al. [22] | 7       | 221     | 15    | 221   | 7.9%   | 0.45 [0.18, 1.12] |
| Zhao et al. [28] | 4       | 60      | 12    | 60    | 5.4%   | 0.29 [0.09, 0.94] |
| Total (95%CI)     |         |         |       |       | 1718   | 1660 | 100.0% | 0.52 [0.38, 0.72] |
| Total events      |         |         |       |       | 129    | 216  |
| Heterogeneity: Tau^2 = 0.11; \( \chi^2 = 18.60, df = 12 (P = 0.10) \); \( I^2 = 35\% \)

Test for overall effect: Z = 4.02 (\( P < 0.0001 \))

### B

| Study or subgroup | Rectal NSAIDs | Placebo |
|------------------|---------------|---------|
|                  | Event | Total | Event | Total | Weight | Odds ratio M-H, Random, 95%CI |
| Doıbrönte et al. [23] | 11   | 130   | 11    | 98    | 15.7%  | 0.73 [0.30, 1.76] |
| Doıbrönte et al. [24] | 20   | 347   | 22    | 318   | 23.1%  | 0.82 [0.44, 1.54] |
| Khoshsbaten et al. [32] | 2    | 50    | 13    | 50    | 6.7%   | 0.12 [0.03, 0.56] |
| Montaño Loza et al. [20] | 3    | 61    | 8     | 56    | 8.1%   | 0.31 [0.08, 1.23] |
| Montaño Loza et al. [20] | 4    | 75    | 12    | 75    | 10.3%  | 0.30 [0.09, 0.96] |
| Murray et al. [28] | 7    | 110   | 17    | 110   | 14.7%  | 0.37 [0.15, 0.94] |
| Otsuka et al. [20] | 2    | 51    | 10    | 53    | 6.5%   | 0.18 [0.04, 0.85] |
| Sotoudehmanesh et al. [22] | 7    | 221   | 15    | 221   | 14.9%  | 0.45 [0.18, 1.12] |
| Total (95%CI)     |         |       |       |       | 1045   | 981  | 100.0% | 0.43 [0.28, 0.67] |
| Total events      |         |       |       |       | 56     | 108  |
| Heterogeneity: Tau^2 = 0.11; \( \chi^2 = 9.86, df = 7 (P = 0.20) \); \( I^2 = 29\% \)

Test for overall effect: Z = 3.77 (\( P = 0.0002 \))

### C

| Study or subgroup | Diclofenac | Placebo |
|------------------|------------|---------|
|                  | Event | Total | Event | Total | Weight | Odds ratio M-H, Random, 95%CI |
| Cheon et al. [26] | 17   | 105   | 17    | 102   | 19.2%  | 0.97 [0.46, 2.02] |
| Khoshsbaten et al. [24] | 2    | 50    | 13    | 50    | 9.9%   | 0.12 [0.03, 0.56] |
| Murray et al. [28] | 7    | 110   | 17    | 110   | 16.6%  | 0.37 [0.15, 0.94] |
| Otsuka et al. [20] | 2    | 51    | 10    | 53    | 9.7%   | 0.18 [0.04, 0.85] |
| Park et al. [28] | 22   | 173   | 20    | 170   | 20.4%  | 1.09 [0.57, 2.09] |
| Senol et al. [20] | 3    | 40    | 7     | 40    | 10.9%  | 0.38 [0.09, 1.60] |
| Zhao et al. [28] | 4    | 60    | 12    | 60    | 13.3%  | 0.29 [0.09, 0.94] |
| Total (95%CI)     |         |       |       |       | 589    | 585  | 100.0% | 0.45 [0.24, 0.83] |
| Total events      |         |       |       |       | 57     | 96   |
| Heterogeneity: Tau^2 = 0.38; \( \chi^2 = 14.49, df = 6 (P = 0.02) \); \( I^2 = 59\% \)

Test for overall effect: Z = 2.55 (\( P = 0.01 \))

### D

| Study or subgroup | Indomethacin | Placebo |
|------------------|--------------|---------|
|                  | Event | Total | Event | Total | Weight | Odds ratio M-H, Random, 95%CI |
| Doıbrönte et al. [23] | 11   | 130   | 11    | 98    | 20.6%  | 0.73 [0.30, 1.76] |
| Doıbrönte et al. [24] | 20   | 347   | 22    | 318   | 40.7%  | 0.82 [0.44, 1.54] |
| Elimunzer et al. [24] | 27   | 295   | 523   | 307   | Not estimable |
| Montaño Loza et al. [20] | 3   | 61    | 8     | 56    | 8.4%   | 0.31 [0.08, 1.23] |
| Montaño Loza et al. [20] | 4   | 75    | 12    | 75    | 11.4%  | 0.30 [0.09, 0.96] |
| Sotoudehmanesh et al. [22] | 7   | 221   | 15    | 221   | 18.9%  | 0.45 [0.18, 1.12] |
| Total (95%CI)     |         |       |       |       | 1129   | 1075 | 100.0% | 0.59 [0.39, 0.88] |
| Total events      |         |       |       |       | 72     | 591  |
| Heterogeneity: Tau^2 = 0.00; \( \chi^2 = 3.81, df = 4 (P = 0.43) \); \( I^2 = 0\% \)

Test for overall effect: Z = 2.61 (\( P = 0.009 \))
Sajid MS et al. NSAIDs to prevent post-ERCP pancreatitis

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

---

E

| Study or subgroup | NSAIDs Event | Total | Placebo Event | Total | Weight | Odds ratio M-H, Random, 95%CI | Odds ratio M-H, Random, 95%CI |
|------------------|-------------|-------|---------------|-------|--------|--------------------------------|--------------------------------|
| Dobrónté et al[29] | 11          | 130   | 11            | 98    | 19.9%  | 0.73 [0.30, 1.76]              |                                |
| Dobrónté et al[29] | 20          | 347   | 22            | 318   | 33.1%  | 0.82 [0.44, 1.54]              |                                |
| Montañol Loza et al[31] | 3       | 61    | 8             | 56    | 9.1%   | 0.31 [0.08, 1.23]              |                                |
| Montañol Loza et al[31] | 4       | 75    | 12            | 75    | 12.1%  | 0.30 [0.09, 0.96]              |                                |
| Otsuka et al[32] | 2           | 51    | 10            | 53    | 7.2%   | 0.18 [0.04, 0.85]              |                                |
| Sotoudehmanesh et al[33] | 7       | 221   | 15            | 221   | 18.6%  | 0.45 [0.18, 1.12]              |                                |
| Total (95%CI) | 885         |       | 821            |       | 100.0% | 0.52 [0.34, 0.80]              |                                |

F

| Study or subgroup | NSAIDs Event | Total | Placebo Event | Total | Weight | Odds ratio M-H, Random, 95%CI | Odds ratio M-H, Random, 95%CI |
|------------------|-------------|-------|---------------|-------|--------|--------------------------------|--------------------------------|
| Elmunzer et al[29] | 27          | 295   | 52            | 307   | 27.3%  | 0.49 [0.30, 0.81]              |                                |
| Khoshbaten et al[30] | 2          | 50    | 13            | 50    | 9.0%   | 0.12 [0.03, 0.56]              |                                |
| Murray et al[30] | 7           | 110   | 17            | 110   | 17.3%  | 0.37 [0.15, 0.94]              |                                |
| Park et al[31] | 22          | 173   | 20            | 170   | 23.5%  | 1.09 [0.57, 2.09]              |                                |
| Senol et al[31] | 3           | 40    | 7             | 40    | 10.1%  | 0.38 [0.09, 1.60]              |                                |
| Zhao et al[32] | 4           | 60    | 12            | 60    | 12.9%  | 0.29 [0.09, 0.94]              |                                |
| Total (95%CI) | 728         |       | 737            |       | 100.0% | 0.45 [0.27, 0.77]              |                                |

---

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.
Table 3  Reported quality variables in included studies

| Ref. | Randomization | Power calculations | ITT | Blinding | Concealment |
|------|---------------|--------------------|-----|----------|-------------|
| Cheon et al[31] | Yes | Yes | Yes | Yes | Yes |
| Debrönte et al[32] | Yes | Yes | No | Yes | Yes |
| Debrönte et al[33] | Yes | Yes | No | Yes | Yes |
| Elmunzer et al[34] | Yes | Yes | Yes | Yes | Yes |
| Khoshbaten et al[35] | Yes | Yes | No | Yes | Yes |
| Montaño Loza et al[36] | Yes | Yes | No | Yes | Yes |
| Montaño Loza et al[37] | Yes | Yes | No | Yes | Not reported |
| Murray et al[38] | Yes | Yes | No | Yes | Yes |
| Otsuka et al[39] | Yes | Yes | No | Yes | Yes |
| Park et al[40] | Yes | Yes | No | Yes | Yes |
| Senol et al[41] | Yes | Yes | No | Not reported | Not reported |
| Sotoudehmanesh et al[42] | Yes | Yes | No | Yes | Yes |
| Zhao et al[43] | Yes | Yes | No | No | Not reported |

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.

REFERENCES
1. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spiritito F, Piotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 2007; 102: 1781-1788 [PMID: 17509029]
2. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001; 54: 425-434 [PMID: 11577302]
3. Vandervoorst J, Soetikno RM, Tham TC, Wong RC, Ferrari AP, Montes H, Roston AD, Slivka A, Lichtenstein DR, Raymann FW, Van Dam J, Hughes M, Carr-Locke DL. Risk factors for complications after performance of ERCP. Gastrointest Endosc 2002; 56: 652-656 [PMID: 12397271]
4. Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009; 104: 31-40 [PMID:

> 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 contribution 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).

> 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.
Sajid MS et al. NSAIDs to prevent post-ERCP pancreatitis

19098846

5 Sherman S, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Duu KS, Aliperti G, Yakele F, Uzer M, Jones W, Goff J, Earle D, Temkit M, Lehman GA. Prophylactic administration of corticosteroids to reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. Gastrointest Endosc 2003; 58: 23-29 [PMID: 12838216]

Kochar B, Akshintala VS, Afghani E, Elmunzer BJ, Kim KJ, Lennon AM, Khashab MA, Kalloo AN, Singh VK. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015; 81: 143-149.e9 [PMID: 25088919 DOI: 10.1016/j.gie.2014.06.045]

Wong Ll, Tsai Hh. Prevention of post-ERCP pancreatitis. World J Gastrointest Pathophysiol 2014; 5: 1-10 [PMID: 24891970 DOI: 10.4291/wjgpp.v5.i1.1]

Pharmacol Ther 2009; 29: 1078-1085 [PMID: 19236312 DOI: 10.1111/j.1365-2036.2009.03978]

Zheng MH, Bai JL, Meng MB, Chen YP. Gabexate mesylate in the prevention of diclofenac on the levels of lipoxin A4 and Resolvin D1 and E1 [PMID: 25030943 DOI: 10.1007/s10620-014-3280-6]

28 Montaño Loza A, García Correa J, González Ojeda A, Rodríguez Lomeli X. [Prevention of hyperamilasemia and pancreatitis after endoscopic retrograde cholangiopancreatography] Rev Gastroenterol Mex 2008; 23: e11-e16 [PMID: 17683501 DOI: 10.1111/j.1440-1746.2007.00225.x]

Montaño Loza A, García Correa J, Dávalos Cobión C, Rodríguez Lomeli X. [Prevention of hyperamilasemia and pancreatitis after endoscopic retrograde cholangiopancreatography: a systematic review and meta-analysis update]. Gastroenterology 2009; 136: 1414-1422 [PMID: 19744121 DOI: 10.1016/S0016-5085(08)03684-6]

Khoshbaten M, Khorram H, Madad L, Elsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol 2008; 23: e11-e16 [PMID: 17683501 DOI: 10.1111/j.1440-1746.2007.00225.x]

27 Murray B, Carri R, Imrie C, Evans S, O’Sullleabain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003; 124: 1786-1791 [PMID: 12806612 DOI: 10.1016/S0016-5085(03)00836-4]

31 Park SW, Chung MJ, Oh TG, Park JY, Bang S, Park SW, Song SY. Intramuscular diclofenac for the prevention of post-ERCP pancreatitis: a randomized trial. Endoscopy 2015; 47: 33-39 [PMID: 25409167 DOI: 10.1055/s-0034-1390743]

Senol A, Saritas U, Demirkan H. Efficacy of intramuscular diclofenac and fluid replacement in prevention of post-ERCP pancreatitis. World J Gastroenterol 2009; 15: 3999-4004 [PMID: 19705494 DOI: 10.3748/wjg.v15.i39.3999]

Sotudehmanesh R, Khatibi H, Kolahdoozan S, Ainechi M, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007; 102: 978-983 [PMID: 17355281 DOI: 10.1111/j.1572-0241.2007.01165.x]

Zhao XW, Bao JJ, Hu C, Ding H, Liu XC, Mei Q, Xu JM. Effect of diclofenac on the levels of lipoxin A4 and Resolvin D1 and E1 in the post-ERCP pancreatitis. Dig Dis Sci 2014; 59: 2992-2996 [PMID: 25030943 DOI: 10.1007/s00260-014-3280-6]

Kubiliun NM, Adams MA, Akshintala VS, Conte ML, Cote GA, Cotton PB, Dumonceau JM, Elga H, Fogel EL, Freeman ML, Lehman GA, Navede M, Romurguano J, Schieim JM, Singh VK, Elmunzer BJ. Evaluation of Pharmacologic Prevention of Pancreatitis After Endoscopic Retrograde Cholangiopancreatography: A Systematic Review. Clin Gastroenterol Hepatol 2015; 13: 1231-1239; quiz e70-e71 [PMID: 25579870 DOI: 10.1016/j.cgh.2014.11.038]

10.1111/j.1572-0241.2007.01165.x
36 Li X, Tao LP, Wang CH. Effectiveness of nonsteroidal anti-inflammatory drugs in prevention of post-ERCP pancreatitis: a meta-analysis. World J Gastroenterol 2014; 20: 12322-12329 [PMID: 25232268 DOI: 10.3748/wjg.v20.i34.12322]
37 Sun HL, Han B, Zhai HP, Cheng XH, Ma K. Rectal NSAIDs for the prevention of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. Surgeon 2014; 12: 141-147 [PMID: 24332479 DOI: 10.1016/j.surge.2013.10.010]
38 Lerrant Y, D’Angelo Bernard G, Moumni M, Counis R. [Ambivalent effect of thyroxine on the expression of gonadotropin genes in normal and orchidectomized rats]. Pathol Biol (Paris) 1988; 36: 973-978 [PMID: 2462206 DOI: 10.1016/MPA.0000060]
39 Sethi S, Sethi N, Wadhwia V, Garul S, Brown A. A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas 2014; 43: 190-197 [PMID: 24518496 DOI: 10.1097/MPA.0000090]
40 Puig I, Calvet X, Baylina M, Isava Á, Sort P, Llaó J, Porta F, Vida F. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. PLoS One 2014; 9: e92922 [PMID: 24675922 DOI: 10.1371/journal.pone.0092922]
41 Yaghoobi M, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, Szego P, Barkun AN. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. Aliment Pharmacol Ther 2013; 38: 995-1001 [PMID: 24099466 DOI: 10.1111/apt.12488]
42 Akbar A, Abu Duyeh BK, Baron TH, Wang Z, Altayar O, Murad MH. 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: 778-783 [PMID: 23376320 DOI: 10.1016/j.cgh.2012.12.043]
43 Zheng MH, Meng MB, Gu DN, Zhang L, Wu AM, Jiang Q, Chen YP. Effectiveness and tolerability of NSAIDs in the prophylaxis of pancreatitis after endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis. Curr Ther Res Clin Exp 2009; 70: 323-334 [PMID: 24683241 DOI: 10.1016/j.eurtres.2009.08.001]
44 Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. Hepatobiliary Pancreat Dis Int 2009; 8: 11-16 [PMID: 19208508]
45 Ding X, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. Gastrointest Endosc 2012; 76: 1152-1159 [PMID: 23164513 DOI: 10.1016/j.gie.2012.08.021]
46 Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut 2008; 57: 1262-1267 [PMID: 18375470 DOI: 10.1136/gut.2007.140756]
47 Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Plehey AM. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996; 335: 909-918 [PMID: 8782497]

P- Reviewer: Bartlett D, Gornik I, Machado MCC, Vitali F
S- Editor: Ji FF  L- Editor: A  E- Editor: Lu YJ
