Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis

ABSTRACT

Background and study aims Endoscopic retrograde cholangiopancreatography (ERCP) is the primary therapeutic procedure for treatment of diseases that affect the biliary tree and pancreatic duct. While the therapeutic success rate of ERCP is high, the procedure can cause complications, such as acute pancreatitis (PEP), bleeding, and per-
stratifies incidence rates of 3.6% to 4% for mild acute pancreatitis, 1.8% to 2.8% for moderate acute pancreatitis, and 0.3% to 0.5% for severe acute pancreatitis [4,5].

Risk factors for PEP include sex (female), age (30 to 40 years), and history of dysfunction in the sphincter of Oddi, pancreatitis, and biliary tree obstruction [1,2,6]. PEP may increase hospitalization time, drug use, rate of intensive care unit (ICU) admission, and incidence of pancreatic necrosis and edema, pseudocyst formation, inflammation or sepsis, and death (1–3% of patients) [7]. Therefore, prevention of PEP is critical to increasing patient safety and reducing healthcare burden.

Numerous studies have examined preventative measures for PEP, such as use of nonsteroidal anti-inflammatory drugs (NSAIDs) and placement of pancreatic stents. NSAIDs inhibit activation of intrapancreatic proteases, thereby preventing inflammatory cascade and reducing pancreatic lesions [8,9], whereas placement of a pancreatic stent is expected to maintain fluid secretion, which reduces papillary edema [10].

Over the years, numerous families of drugs have been used as prophylactic medications, ranging from protease inhibitors (Pis) to antibiotics, hormonal drugs, antioxidants, heparin and anti-inflammatory cytokines. Drugs used for prevention of acute PEP, including corticosteroids, have been tested [11].

Moreover, the Pl aprotinin (Trasylol) was one of the first agents assayed for PEP [12], and the drug was widely used for PEP in the 1970s and 1980s.

In recent systematic reviews, it is worth noting that recommendations emphasized use of topical epinephrine for the sphincter of Oddi and sublingual nitroglycerin in addition to parallel prescriptions for aggressive use of intravenous fluids [11].

Use of indomethacin, aspirin, and other NSAIDs for treatment of acute pancreatitis has been investigated since the 1980s [13]. Remarkably, indomethacin can induce PEP, although less frequently than cortisone [14].

Considering the anti-inflammatory properties of NSAIDs for papillary edema and PEP, along with controversies about prevention of PEP with use of pharmacologic interventions, we conducted a systematic review and meta-analysis.

The current study aimed to compare efficacy of NSAIDs versus placebo in prevention of acute PEP after ERCP.

Materials and methods
Protocol and registry
This systematic review and meta-analysis was performed in accordance with recommendations in the Cochrane Handbook, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. The review was registered in PROSPERO international database under the number 42016049582.

Eligibility criteria and search procedure
Only randomized controlled trials (RCTs) that assessed use of NSAIDs in preventing PEP were included. There was no restriction with regard to language and date of publication. Studies including use of pancreatic stents were excluded. Patients older than 18 years who underwent their first ERCP were included. Studies with alternative groups of patients were excluded from the analysis. NSAIDs and placebo were administered in the RCTs.

The primary outcome of the studies selected was incidence of PEP. Secondary outcomes were severity of pancreatitis (mild, moderate, and severe), route of administration (rectal, intramuscular [IM], intravenous [IV], and oral), and types of NSAIDs (indomethacin, diclofenac, and others).

We thoroughly searched databases, such as MEDLINE, Embase, and Cochrane Central Library, from the start of the study until October 1, 2017.

The keywords used in searching MEDLINE were as follows: (Retrograde Cholangiopancreatography, Endoscopic OR Cholangiopancreatographies, Endoscopic Retrograde OR Endoscopic Retrograde Cholangiopancreatographies OR Retrograde Cholangiopancreatographies, Endoscopic OR Endoscopic Retrograde Cholangiopancreatography OR ERCP) AND (Pancreatitis) AND (AINS OR Diclofenaco OR Indomethacin OR Naproxen). For other databases, we combined simpler terms, such as ERCP AND Pancreatitis AND NSAID.

Evaluation of eligibility criteria and selection of studies were performed independently by two reviewers. Any disagreement
was resolved by the authors after reaching a consensus. The selection process is outlined in the PRISMA flow chart [15]. Each study was classified according to risk of bias, which considered clinical questions, randomization, allocation, blinding, loss to follow-up, prognostic factors, outcomes, and intention to treat analysis. We also used the JADAD scale (Jadad et al. 1996) [16], which considers randomization, blinding of patients and investigators, and description of exclusion and losses.

**Data analysis**

Data were extracted based on intention to treat information. Absolute numbers, means and standard deviations were used for quantitative analysis. For every outcome and subgroup analysis, we calculated the RD with 95% CI, and a \( P<0.05 \) was considered significant. Analyses were carried out using RevMan 5.3 software. Due to the heterogeneity of studies, a statistical analysis using a random effect model was performed.

**Results**

Twenty-one RCTs were considered eligible with a total of 6854 patients analyzed. Of the patients, 3427 used NSAIDs before ERCP (intervention) and 3427 did not use the drugs (control group) (Fig. 1).

With regard to route of administration, NSAIDs were administered via the rectum, IV, IM, and per OS in 12, three, one, and two studies, respectively. The following NSAIDs were used: diclofenac [17–28], indomethacin [11, 29–34], naproxen [35], valdecoxib [8], and ketoprofen [36]. Study characteristics are outlined in Table 1.

In assessment of risk of bias, all articles presented adequate randomization, allocation, and blinding. Losses occurred in five RCTs. However, the value did not reach 20%. In all studies, the JADAD score was above 3, which is satisfactory for inclusion in this systematic review. The bias assessment summary is outlined in Table 2.

Time to diagnose in individuals with PEP varied among studies from 90 minutes to 72 hours post-ERCP, and patients met at least two of the three major diagnostic criteria: history of abdominal pain, increase in amylase level, and imaging study results consistent with PEP.

| Reference                  | Year | Country  | Administration | Single dose | Type of NSAID |
|----------------------------|------|----------|----------------|-------------|---------------|
| Andrade et al. 2015 [28]   | 2015 | México   | Rectal         | 100 mg      | Indomethacin  |
| Bhatia et al. 2011 [5]     | 2011 | India    | Intravenous    | 20 mg       | Valdecoxib   |
| Cheon et al. 2007 [25]     | 2007 | USA      | Oral           | 50 mg       | Diclofenac   |
| Döbrönte et al. 2014 [30]  | 2014 | Hungary  | Rectal         | 100 mg      | Indomethacin |
| Elmunzer et al. 2012 [14]  | 2012 | USA      | Rectal         | 100 mg      | Indomethacin |
| Hauser et al. 2016 [19]    | 2016 | Croatia  | Rectal         | 100 mg      | Diclofenac   |
| Ishiwatari et al. 2016 [17]| 2016 | Japan    | Oral           | 100 mg      | Diclofenac   |
| Khoshbaten et al. 2008 [21]| 2008 | Irán     | Rectal         | 50 mg       | Diclofenac   |
| Leerhoy et al. 2016 [18]   | 2016 | Denmark  | Rectal         | 100 mg      | Diclofenac   |
| Levenick et al. 2016 [29]  | 2016 | USA      | Rectal         | 100 mg      | Indomethacin |
| Lua et al. 2015 [15]       | 2015 | Malaysia | Rectal         | 100 mg      | Diclofenac   |
| Mansour et al. 2016 [32]   | 2016 | Irán     | Rectal         | 500 mg      | Naproxen     |
| Montaño et al. 2007 [27]   | 2007 | México   | Rectal         | 100 mg      | Indomethacin |
| Mousalreza et al. 2016 [31]| 2016 | Irán     | Rectal         | 100 mg      | Indomethacin |
| Murray et al. 2003 [24]    | 2003 | Scotland | Rectal         | 100 mg      | Diclofenac   |
| Otsuka et al. 2012 [23]    | 2012 | Japan    | Rectal         | 50 mg       | Diclofenac   |
| Park et al. 2014 [16]      | 2014 | Korea    | Intramuscular  | 100 mg      | Diclofenac   |
| Patai et al. 2015 [26]     | 2015 | Hungary  | Rectal         | 100 mg      | Indomethacin |
| Quadros et al. 2016 [33]   | 2016 | Brazil   | Intravenous    | 100 mg      | Ketoprofen   |
| Senol et al. 2009 [20]     | 2009 | USA      | Intravenous    | 50 mg       | Diclofenac   |
| Uçar et al. 2016 [22]      | 2016 | Turkey   | Intramuscular and rectal | 75–100 mg | Diclofenac |
Incidence of post-ERCP pancreatitis

All 21 articles assessed incidence of PEP and compared 3427 patients in each group. In total, 250 events were observed in the NSAID group and 407 in the control group. The RD was $-0.05$ (95% CI, $-0.07$ to $-0.03$; $P<0.05$). The number needed to treat (NNT) was 20. Forest plots of the incidence of post-ERCP PEP are shown in Fig. 2.

Severity of pancreatitis

Mild pancreatitis

Patients presented with mild pancreatitis in 14 of the 21 studies. In total, 136 of 2600 patients and 203 of 2569 patients in the NSAID and control groups, respectively, presented with the condition. Incidence of mild pancreatitis in the intervention group decreased, with an RD of $-0.03$ (95% CI, $-0.05$ to $-0.01$; $P<0.05$). The NNT was 33.

Moderate pancreatitis

Patients presented with moderate pancreatitis in 11 of 21 RTCs. In total, 54 of 2134 patients and 89 of 2150 patients in the NSAID and control groups, respectively, had the condition. The RD was $-0.01$ (95% CI, $-0.02$ to 0.00; $P>0.05$).

Severe pancreatitis

Patients presented with severe pancreatitis in seven of 21 studies. In total, 16 of 1740 patients and 23 of 1747 patients in the NSAID and control groups, respectively, had the condition. No statistical difference was observed between the methods with RD $-0.00$ (95% CI, $-0.01$ to 0.00; $P>0.05$).

Forest plots summarizing the analyses of the severity of the pancreatitis are shown in Fig. 3.

Routes of administration

With regard to routes of drug administration, rectal administration was the most commonly used route. In 15 studies, 4988 patients preferred rectal administration. In total, 170 of 2492 patients in the NSAID group and 324 of 2496 patients in the control group presented with PEP. The RD was $-0.07$ (95% CI, $-0.10$ to $-0.04$; $P<0.05$). The NTT was 20.

Table 2: Descriptive table of the studies.

| Author            | Randomization | Allocation | Blinding | Losses | Prognosis | IIT | JADAD |
|-------------------|---------------|------------|----------|--------|-----------|-----|-------|
| Andrade et al. 2015 [28] | Yes           | Yes        | No       | No     | Homogeneous | Yes | 3     |
| Bhatia et al. 2011 [5]     | Yes           | Yes        | No       | No     | Homogeneous | No  | 3     |
| Cheon et al. 2007 [25]     | Yes           | Yes        | Yes      | Yes    | Homogeneous | No  | 5     |
| Döbrönte et al. 2014 [30]  | Yes           | No         | No       | Yes    | Homogeneous | No  | 3     |
| Elmunzer et al. 2012 [14]  | Yes           | Yes        | Yes      | No     | Homogeneous | Yes | 5     |
| Hauser et al. 2016 [19]    | Yes           | Yes        | Yes      | No     | Homogeneous | Yes | 5     |
| Ishiwatari et al. 2016 [17] | Yes          | Yes        | Yes      | Yes    | Homogeneous | No  | 3     |
| Khoshbaten et al. 2008 [21] | Yes          | Yes        | Yes      | No     | Homogeneous | No  | 5     |
| Leehroy et al. 2016 [18]   | Yes           | No         | No       | No     | Homogeneous | No  | 3     |
| Levenick et al. 2016 [29]  | Yes           | Yes        | Yes      | No     | Homogeneous | Yes | 5     |
| Lua et al. 2015 [15]       | Yes           | Yes        | No       | Yes    | Homogeneous | Yes | 3     |
| Mansour et al. 2016 [32]   | Yes           | Yes        | Yes      | No     | Homogeneous | Yes | 4     |
| Montaño et al. 2007 [27]   | Yes           | No         | Yes      | No     | Homogeneous | No  | 3     |
| Mousalreza et al. 2016 [31] | Yes          | Yes        | Yes      | No     | Homogeneous | No  | 3     |
| Murray et al. 2003 [24]    | Yes           | Yes        | Yes      | No     | Homogeneous | No  | 3     |
| Otsuka et al. 2012 [23]    | Yes           | No         | No       | No     | Homogeneous | Yes | 3     |
| Park et al. 2014 [16]      | Yes           | Yes        | Yes      | No     | Homogeneous | No  | 3     |
| Patai et al. 2015 [26]     | Yes           | Yes        | Yes      | Yes    | Homogeneous | Yes | 5     |
| Quadros et al. 2016 [33]   | Yes           | Yes        | Yes      | No     | Homogeneous | Yes | 5     |
| Senol et al. 2009 [20]     | Yes           | No         | No       | No     | Homogeneous | No  | 3     |
| Uçar et al. 2016 [22]      | Yes           | No         | No       | No     | Homogeneous | Yes | 3     |
Six studies that used other administration routes (PO, IV, and IM) have reported that 80 of 935 patients and 83 of 931 patients in the NSAID and control groups, respectively, presented with PEP. The RD was \(-0.00\) (95% CI, \(-0.02\) to \(0.02\); \(P > 0.05\)).

Routes of administration and associated efficacies are summarized in ▶ Fig. 4.

**Types of NSAIDs**

In 11 studies, diclofenac was used, and PEP was observed in 121 of 1421 patients in the NSAID group and 184 of 1403 patients in the control group. The RD was \(-0.05\) (95% CI, \(-0.09\) to \(-0.02\); \(P < 0.05\)).

Seven RCTs evaluated efficacy of indomethacin in preventing PEP. In total, 100 of 1493 patients in the NSAID group and 178 of 1484 patients in the control group presented with PEP. The RD was \(-0.06\) (95% CI, \(-0.10\) to \(-0.02\); \(P < 0.05\)) and the NNT was 17.

In three studies, other NSAIDs (valdecoxib, naproxen, and ketoprofen) were used for prevention of PEP. In total, 29 of 513 patients and 45 of 542 patients in the NSAID and control groups, respectively, presented with PEP. The RD was \(-0.03\) (95% CI, \(-0.09\) to \(0.03\); \(P > 0.05\)) and the NNT was 20.

▶ Fig. 5 summarizes the meta-analysis on types of NSAIDs.

**Discussion**

The impact of periprocedural NSAIDs during ERCP has been extremely compelling within the last 4 to 5 years. Although the results were conflicting, major international societies have endorsed their routine prescription. The European Society of Comparative Gastroenterology recommends administering NSAIDs (diclofenac or indomethacin 100 mg) rectally before or after ERCP if no contraindications are observed [37]. Analogously, the American Society for Gastrointestinal Endoscopy [38] is in favor of administration of NSAIDs after contraindications have been ruled out. However, this is only applicable in high-risk individuals. Meanwhile, use of indomethacin for average-risk patients is also recommended.

As regards the Japanese Guidelines by the Japanese Ministry of Health, they advocate a similar policy for intrarectal adminis-
### 4.1.1 Mild pancreatitis

| Study or subgroup | NSAI Ds | Place b o o | Risk difference |
|------------------|---------|------------|----------------|
|                  | Events | Total | Events | Total | Weight | M-H, random, 95 % Cl | Risk difference |
| Andrade et al., 2015 | 1     | 82    | 16    | 84    | 0.8 % | – 0.18 [– 0.27, – 0.09] |
| Cheon et al., 2007   | 2       | 105   | 11    | 102   | 0.9 % | – 0.01 [– 0.09, 0.07] |
| Döbrönte et al., 2016 | 16     | 347   | 18    | 318   | 3.3 % | – 0.01 [– 0.04, 0.02] |
| Elmunzer et al., 2012 | 2       | 295   | 26    | 307   | 2.7 % | – 0.04 [– 0.08, 0.00] |
| Hauser et al., 2016   | 9       | 129   | 16    | 143   | 1.2 % | – 0.04 [– 0.11, 0.03] |
| Ishiwatari et al., 2016 | 13   | 216   | 11    | 214   | 2.4 % | 0.01 [0.03, 0.05] |
| Leer hoy et al., 2016 | 8       | 378   | 15    | 394   | 4.6 % | – 0.02 [– 0.04, 0.01] |
| Levenick et al., 2016 | 16     | 223   | 9     | 226   | 2.5 % | 0.03 [0.01, 0.07] |
| Lua et al., 2015      | 4       | 69    | 4     | 75    | 1.0 % | 0.00 [– 0.07, 0.08] |
| Mansour et al., 2016  | 8       | 162   | 18    | 162   | 1.6 % | – 0.06 [– 0.12, – 0.00] |
| Otsuka et al., 2012   | 2       | 51    | 7     | 53    | 0.6 % | – 0.09 [– 0.20, 0.01] |
| Park et al., 2014     | 19      | 173   | 18    | 172   | 1.3 % | 0.01 [0.06, 0.07] |
| Patai et al., 2015    | 15      | 270   | 25    | 269   | 2.2 % | – 0.06 [– 0.11, – 0.01] |
| Uçar et al., 2016     | 1       | 100   | 3     | 50    | 1.2 % | – 0.05 [– 0.12, 0.02] |
| **Subtotal (95 % CI)** | 2600   | 2569  | 26.3 % | – 0.03 [– 0.05, – 0.01] |

Total events 136  203
Heterogeneity: Tau² = 0.00; Chi² = 30.27, df = 13 (P = 0.004); I² = 57 %
Test for overall effect: Z = 2.58 (P = 0.010)

### 4.1.2 Moderate

| Study or subgroup | NSAI Ds | Place b o o | Risk difference |
|------------------|---------|------------|----------------|
|                  | Events | Total | Events | Total | Weight | M-H, random, 95 % Cl | Risk difference |
| Andrade et al., 2015 | 3     | 82    | 1     | 84    | 2.2 % | 0.02 [0.02, 0.07] |
| Cheon et al., 2007   | 6       | 105   | 5     | 102   | 1.5 % | 0.01 [– 0.05, 0.07] |
| Elmunzer et al., 2012 | 10    | 295   | 24    | 307   | 3.0 % | – 0.04 [– 0.08, – 0.01] |
| Hauser et al., 2016   | 1       | 129   | 4     | 143   | 3.6 % | – 0.02 [– 0.05, 0.01] |
| Ishiwatari et al., 2016 | 6     | 216   | 4     | 214   | 3.9 % | 0.01 [– 0.02, 0.04] |
| Leer hoy et al., 2016 | 15     | 378   | 25    | 394   | 3.6 % | – 0.02 [– 0.05, 0.01] |
| Mansour et al., 2016  | 4       | 162   | 10    | 162   | 2.4 % | – 0.04 [– 0.08, 0.01] |
| Park et al., 2014     | 1       | 173   | 2     | 172   | 5.2 % | – 0.01 [– 0.03, 0.01] |
| Patai et al., 2015    | 2       | 270   | 5     | 269   | 5.3 % | – 0.01 [– 0.03, 0.01] |
| Quadros et al., 2016  | 5       | 224   | 5     | 253   | 4.3 % | 0.00 [0.02, 0.03] |
| Uçar et al., 2016     | 1       | 100   | 4     | 50    | 1.0 % | – 0.07 [– 0.15, 0.01] |
| **Subtotal (95 % CI)** | 2134   | 2150  | 35.9 % | – 0.01 [– 0.02, 0.00] |

Total events 54  89
Heterogeneity: Tau² = 0.00; Chi² = 15.19, df = 10 (P = 0.13); I² = 34 %
Test for overall effect: Z = 1.87 (P = 0.06)

### 4.1.3 Severe pancreatitis

| Study or subgroup | NSAI Ds | Place b o o | Risk difference |
|------------------|---------|------------|----------------|
|                  | Events | Total | Events | Total | Weight | M-H, random, 95 % Cl | Risk difference |
| Cheon et al., 2007   | 1       | 105   | 1     | 102   | 4.2 % | – 0.00 [– 0.03, 0.03] |
| Döbrönte et al., 2016 | 4     | 347   | 4     | 318   | 5.7 % | – 0.00 [– 0.02, 0.02] |
| Elmunzer et al., 2012 | 3       | 295   | 3     | 307   | 5.8 % | 0.00 [– 0.02, 0.02] |
| Hauser et al., 2016   | 1       | 129   | 1     | 143   | 5.1 % | 0.00 [– 0.02, 0.02] |
| Ishiwatari et al., 2016 | 1     | 216   | 4     | 214   | 5.1 % | – 0.01 [– 0.03, 0.01] |
| Leer hoy et al., 2016 | 5       | 378   | 9     | 394   | 5.3 % | – 0.01 [– 0.03, 0.01] |
| Patai et al., 2015    | 1       | 270   | 1     | 269   | 6.6 % | – 0.00 [– 0.01, 0.01] |
| **Subtotal (95 % CI)** | 1740   | 1747  | 37.7 % | – 0.00 [– 0.01, 0.00] |

Total events 16  23
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 6 (P = 0.86); I² = 0 %
Test for overall effect: Z = 0.76 (P = 0.45)

**Total (95% CI) 6474  6466 100.0 % – 0.01 [– 0.02, – 0.00]**

Total events 206  315
Heterogeneity: Tau² = 0.00; Chi² = 69.12, df = 31 (P < 0.0001); I² = 55 %
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Chi² = 6.18, df = 2 (P = 0.05), I² = 67.7 %

> Fig. 3 Forest plots assessing NSAID efficacy according to pancreatitis severity.
tation of NSAIDs in all cases of ERCP with no contraindications [39]. The current study is based on these foundations with consideration for several unclear details.

Unlike other systematic reviews on use of NSAIDs to reduce risk of developing PEP [3, 40, 41], the current study included only RCTs in which a subgroup analysis was conducted of the efficacy of such medications according to the severity of PEP, administration route, and drug type. Pooled results of these 21 randomized studies showed a significant reduction in risk of developing PEP with use of NSAIDs. However, the effect was restricted to mild cases. Furthermore, these studies showed the efficacy of rectal administration of diclofenac and indomethacin.

Due to the scarce number of randomized studies published in the literature, it was not possible to identify whether other NSAID administration routes are effective in preventing PEP beyond the rectal route and we consider this a limitation of our study. Large RCTs and multicenter studies are needed comparing administration techniques for these NSAIDs as well as other different types of NSAIDs for evaluation and comparison of efficacy in preventing PEP post-ERCP.

Rectal administration of NSAIDs is the most commonly used method for preventing PEP. A standard recommended dose has not been established, although most studies used 100 mg daily. Rectal administration of diclofenac or indomethacin using this dose is highly effective for prevention of PEP. Physicians performing ERCP will decide what drug to use. However, their decisions may also be influenced by cost because indomethacin is more expensive than diclofenac. A cost comparison of NSAIDs for decreasing incidence of PEP must be conducted.

To the best of our knowledge, this is the first meta-analysis on prevention of PEP with use of NSAIDs, which include all

| Study or subgroup | NSAIDs | Placebo | Risk difference | Risk difference |
|-------------------|--------|---------|----------------|----------------|
|                   | Events | Total   | Events | Total | Weight | IV, random, 95% CI | IV, random, 95% CI |
| 3.1.1 Rectal administration |        |         |        |        |         |                      |                      |
| Andrade et al., 2015 | 4 | 82 | 17 | 84 | 3.5% | 0.15 [-0.25, -0.06] |                      |
| Döbrönte et al., 2014 | 20 | 347 | 22 | 318 | 7.0% | -0.01 [-0.05, 0.03] |                      |
| Elmunzer et al., 2012 | 27 | 295 | 52 | 307 | 5.9% | -0.08 [-0.13, -0.02] |                      |
| Hauser et al., 2016 | 11 | 129 | 21 | 143 | 4.5% | -0.06 [-0.14, 0.01] |                      |
| Khoshbaten et al., 2008 | 2 | 50 | 13 | 50 | 2.3% | -0.22 [-0.35, -0.09] |                      |
| Leehoy et al., 2016 | 28 | 378 | 49 | 394 | 6.7% | -0.05 [-0.09, -0.01] |                      |
| Levenick et al., 2016 | 16 | 223 | 11 | 226 | 6.5% | 0.02 [-0.02, 0.07] |                      |
| Lua et al., 2015 | 7 | 69 | 4 | 75 | 3.9% | 0.05 [-0.04, 0.14] |                      |
| Mansour et al., 2016 | 12 | 162 | 28 | 162 | 4.8% | -0.10 [-0.17, -0.03] |                      |
| Montaño et al., 2007 | 4 | 75 | 12 | 75 | 3.5% | -0.11 [-0.20, -0.01] |                      |
| Mousalzadeh et al., 2016 | 11 | 201 | 27 | 205 | 5.7% | -0.08 [-0.13, -0.02] |                      |
| Murray et al., 2003 | 7 | 110 | 17 | 110 | 4.2% | -0.09 [-0.17, -0.01] |                      |
| Otsuka et al., 2012 | 2 | 51 | 10 | 53 | 2.7% | -0.15 [-0.27, -0.03] |                      |
| Patai et al., 2015 | 18 | 270 | 37 | 269 | 6.1% | -0.07 [-0.12, -0.02] |                      |
| Üçar et al., 2016 | 1 | 50 | 4 | 25 | 1.9% | -0.14 [-0.29, 0.01] |                      |
| Subtotal (95% CI) | 2492 | 2496 | 69.2% | 0.07 [-0.10, -0.04] |                      |
| Total events | 170 | 324 | | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 41.02, df = 14 (P = 0.0002); I² = 66% |
| Test for overall effect: Z = 4.46 (P < 0.00001) |

3.1.2 Other administration of NSAIDs

| Study or subgroup | NSAIDs | Placebo | Risk difference | Risk difference |
|-------------------|--------|---------|----------------|----------------|
|                   | Events | Total   | Events | Total | Weight | IV, random, 95% CI | IV, random, 95% CI |
| Bhatia et al., 2011 | 12 | 127 | 12 | 127 | 4.7% | 0.00 [-0.07, 0.07] |                      |
| Cheon et al., 2007 | 17 | 105 | 17 | 102 | 3.3% | -0.00 [-0.11, 0.10] |                      |
| Ishiwatari et al., 2016 | 20 | 216 | 19 | 214 | 5.8% | -0.00 [-0.05, 0.06] |                      |
| Park et al., 2014 | 22 | 173 | 20 | 170 | 4.9% | -0.01 [-0.06, 0.08] |                      |
| Quadros et al., 2016 | 5 | 224 | 5 | 253 | 7.6% | 0.00 [-0.02, 0.03] |                      |
| Senol et al., 2009 | 3 | 40 | 7 | 40 | 2.1% | -0.10 [-0.24, 0.04] |                      |
| Üçar et al., 2016 | 1 | 50 | 3 | 25 | 2.3% | -0.10 [-0.23, 0.03] |                      |
| Subtotal (95% CI) | 935 | 931 | 30.8% | 0.00 [-0.02, 0.02] |                      |
| Total events | 80 | 83 | | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 6 (P = 0.66); I² = 0% |
| Test for overall effect: Z = 0.15 (P = 0.88) |

Total (95% CI) 3427 3427 100.0% -0.05 [-0.07, -0.03]

Total events 250 407
Heterogeneity: Tau² = 0.00; Chi² = 59.23, df = 21 (P < 0.0001); I² = 65% |
Test for overall effect: Z = 4.13 (P < 0.0001) |
Test for subgroup differences: Chi² = 12.99, df = 1 (P = 0.0003), I² = 92.3% | ▶ Fig. 4 Forest plots assessing PEP according to route of drug administration and NSAID type.
types of such drugs (diclofenac, indomethacin, naproxen, valdecoxsib, and ketoprofen). Both diclofenac and indomethacin are highly effective. The putative mechanism of action of these agents is inhibition of phospholipase A2, which leads to a decrease in the inflammatory cascade and downregulation of pro-inflammatory factors, such as leukotrienes, prostaglandins, and platelet-activating agents, and this mechanism reduced inflammatory lesions and organ necrosis [8, 9]. Thus, lack of efficacy of other agents may result in reduced target inhibition with the dose used or pharmacokinetics that are disadvantageous. Nonetheless, the efficacy of other NSAIDs must be further investigated.

It is important to emphasize that our results may have been influenced by confounders, such as the experience of endoscopists, the endoscopic devices used, technical level and extent of nursing care, sedation method, and the type and amount of contrast agent used in the biliary tract. Moreover, several demographic factors influence risk of developing PEP, including sex (female), younger age, and obesity. Thus, patient sex ratio, age, and body mass index may have influenced overall incidence in the individual RCTs. Furthermore, risk for PEP increased with presence of specific diseases (dysfunction of the sphincter of Oddi, cholelithiasis, biliary tract, and pancreatic tumors). Future studies must include both intervention

| Study or subgroup | NSAIDs | Placebo | Risk difference | Risk difference |
|------------------|--------|---------|---------------|---------------|
|                  | Events | Total   | Events | Total | IV, random, 95 % CI | IV, random, 95 % CI |
| **2.1.1 Diclofenac** |        |         |        |       |                      |                      |
| Cheon et al., 2007 | 17  105 | 17  102 | 3.4 % | – 0.00 [– 0.11, 0.10] |                      |                      |
| Hauser et al., 2016 | 11  129 | 21  143 | 4.6 % | – 0.06 [– 0.14, 0.01] |                      |                      |
| Ishiwatari et al., 2016 | 20  216 | 19  214 | 5.9 % | 0.00 [– 0.05, 0.06] |                      |                      |
| Koshbaten et al., 2008 | 2  50 | 13  50 | 2.3 % | – 0.22 [– 0.35, 0.09] |                      |                      |
| Leerhoy et al., 2016 | 28  378 | 49  394 | 6.7 % | – 0.05 [– 0.09, 0.01] |                      |                      |
| Lua et al., 2015 | 7  69 | 4  75 | 4.0 % | 0.05 [– 0.04, 0.14] |                      |                      |
| Murray et al., 2003 | 7  110 | 17  110 | 4.3 % | – 0.09 [– 0.17, 0.01] |                      |                      |
| Otsuka et al., 2012 | 2  51 | 10 | 3.4 % | – 0.15 [– 0.27, 0.03] |                      |                      |
| Park et al., 2014 | 22  173 | 20  170 | 4.9 % | 0.01 [– 0.06, 0.08] |                      |                      |
| Senol et al., 2009 | 3  40 | 7  40 | 2.1 % | – 0.10 [– 0.24, 0.04] |                      |                      |
| Uçar et al., 2016 | 2  100 | 7  50 | 3.4 % | – 0.12 [– 0.22, 0.02] |                      |                      |
| **Subtotal (95 % CI)** | 1421 | 1401 | 44.3 % | – 0.05 [– 0.09, 0.02] |                      |                      |
| Total events | 121 | 184 | | | Test for overall effect: Z = 2.73 (P = 0.006) |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 24.25, df = 10 (P = 0.007); I^2 = 59 %

| **2.1.2 Indomethacin** |        |         |        |       |                      |                      |
| Andrade et al., 2015 | 4  82 | 17  84 | 3.5 % | – 0.15 [– 0.25, 0.06] |                      |                      |
| Döbrönte et al., 2014 | 20  347 | 22  318 | 7.0 % | – 0.01 [– 0.05, 0.03] |                      |                      |
| Elmunzer et al., 2012 | 27  295 | 52  307 | 5.9 % | – 0.08 [– 0.13, 0.02] |                      |                      |
| Levenick et al., 2016 | 16  223 | 11  226 | 6.5 % | 0.02 [– 0.02, 0.07] |                      |                      |
| Montaño et al., 2007 | 4  75 | 12  75 | 3.5 % | – 0.11 [– 0.20, 0.01] |                      |                      |
| Mousalreza et al., 2016 | 11  201 | 27  205 | 5.8 % | – 0.08 [– 0.13, 0.02] |                      |                      |
| Patai et al., 2015 | 18  270 | 37  269 | 6.1 % | – 0.07 [– 0.12, 0.02] |                      |                      |
| **Subtotal (95 % CI)** | 1493 | 1484 | 38.4 % | – 0.06 [– 0.10, 0.02] |                      |                      |
| Total events | 100 | 178 | | | Test for overall effect: Z = 2.78 (P = 0.006) |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 22.17, df = 6 (P = 0.001); I^2 = 73 %

| **2.1.3 Other NSAIDs** |        |         |        |       |                      |                      |
| Bhatia et al., 2011 | 12  127 | 12  127 | 4.8 % | 0.00 [– 0.07, 0.07] |                      |                      |
| Mansour et al., 2016 | 12  162 | 28  162 | 4.9 % | – 0.10 [– 0.17, 0.03] |                      |                      |
| Quadros et al., 2016 | 5  224 | 5  253 | 7.6 % | 0.00 [– 0.02, 0.03] |                      |                      |
| **Subtotal (95 % CI)** | 513 | 542 | 17.3 % | – 0.03 [– 0.09, 0.03] |                      |                      |
| Total events | 29 | 45 | | | Test for overall effect: Z = 0.88 (P = 0.38) |

Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.00, df = 2 (P = 0.03); I^2 = 71 %

Total (95 % CI) | 3427 | 3427 | 100.0 % | – 0.05 [– 0.07, 0.03] |                      |                      |
| Total events | 250 | 407 | | | Test for overall effect: Z = 4.05 (P < 0.0001) |
| Test for subgroup differences: Chi^2 = 59.18, df = 20 (P < 0.00001); I^2 = 66 % |

Test for overall effect: Z = 4.05 (P < 0.0001) |
Test for subgroup differences: Chi^2 = 74.74, df = 2 (P = 0.69), I^2 = 0 %

▶ Fig. 5 Forest plots assessing types of NSAIDs used to prevent PEP.
and control groups. In addition, diagnosis of PEP and its changes post-ERCP showed a substantial heterogeneity among the studies, which included time of evaluation after the procedure (from 90 minutes to 72 hours), clinical symptoms (pain, nausea, and vomiting), and use of imaging data (tomography) [11, 18 – 36, 41].

Another limitation of our manuscript was that not all RCTs stratified the degree of pancreatitis, and when they did, it was not standardized and uniform. A total of 657 cases of PEP was reported (with and without use of NSAIDs). For 521 patients, the degree of pancreatitis involvement was specified. In 339 of these cases, patients were defined as having mild intensity pancreatitis, which represents a total of 65% of the stratified patients (339/521). Thus, our results demonstrated that NSAID use is superior for prevention in patients who developed mild PEP post-ERCP.

Finally, the current systematic review focused only on incidence of PEP and its intensity. However, other complications that affect patient outcome after ERCP, such as perforations and bleeding, were not evaluated.

Nonetheless, this systematic review showed that rectal administration of diclofenac and indomethacin are effective in preventing acute PEP after ERCP. Compared to other methods used to prevent PEP, such as use of pancreatic stents [42, 43], NSAIDs are more convenient to administer, and such drugs are less expensive. Reducing incidence of PEP not only increases patient safety but also reduces healthcare burden by decreasing the rate of hospitalization and ICU stay.

Conclusion

Rectal administration of NSAIDs adequately reduces incidence of acute PEP after ERCP. Mild pancreatitis is the only preventable outcome. In this context, both diclofenac and indomethacin are considered effective. Further RCTs are needed to compare efficacy between NSAID administration pathways in prevention of acute pancreatitis after ERCP.

Competing interests

None

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