WORLD JOURNAL OF GASTROINTESTINAL ENDOSCOPY

Dear Dr.

Thank you very much for your attention and response regarding our work and I will respond in accordance with the indications, rectifications and doubts that you have regarding our work.

We sent you two files, one with the original and the other showing the changes made in red.

1.- Analysis of medication doses: withdrawn

2.- References: changes were made to the references: Full names of authors, DOI and PMID. We will not be able to provide the PMDI with one reference because they are in an article from a university magazine and a chapter presented in a book here in Brazil.

Regarding the references of recent publications, you inform that our work has the last reference of 2016.
I apologize for not posting the corresponding articles for 2017 and 2019, this articles were selected and updated for our analysis in this manuscript.

3.- The request for self-citation was made as you required

4.- Our group is grateful to you for accepting our English and agreeing that we meet all the standards requested by the magazine.

5.- The data requested in power point were performed: showing screenshots of the Revman 5.3 statistical software as well as the original images shown in our work.
Our analyzes were also placed with respect to the data in the descriptive tables and JADAD. Dear Dr., due to the fact that the present manuscript required very hard work, it was done in Portuguese, after that, a summary was made for it to be translated and checked by an English teacher

6.- As requested by you, the highlights were realized

7.- In addition, we placed the funnel plot that we forgot to send to you and made few corrections.

8.- Dear editor, I kindly ask you to add Dr. Otavio Micelli Neto as a member of our ERCP and EUS group.

9.- We add the Funel plot, so there is more cientific evidence of our manuscript.

Name of Journal: World Journal of Gastrointestinal Endoscopy

Manuscript Type: SYSTEMATIC REVIEW AND META-ANALYSIS

Nonsteroidal anti-inflammatory drug effectivity in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: Systematic review and meta-analysis

Juan Pablo Román Serrano[1], José Jukemura[1], Samuel Galante Romanini[2], Paúl Fernando Guamán Aguilar[3], Juliana Silveira Lima de Castro[2], Isabela Trindade Torres[2], José Andres Sanchez Pulla[4], Otavio Micelli Neto, Eloy Taglieri[2], José Celso Ardengh[5]

1.- Department of Gastroenterology, University of Sao Paulo, Sao Paulo, Brazil

2.- Department of Gastrointestinal Endoscopy. Hospital 9 de Julho, Sao Paulo, Brazil

3.- Catholic University of Cuenca, Cuenca, Ecuador

4.- University of Cuenca, Cuenca, Ecuador

5.- University of Sao Paulo, Riberao Preto, and Department of Gastrointestinal Endoscopy. Hospital 9 de Julho, Sao Paulo, Brazil

ORCID Number: Juan Pablo Román Serrano (0000-0002-0453-5323), José Jukemura (0000-0002-3943-7088), Paul Fernando Guamán Aguilar (0000-0002-6813-2814), Samuel Galante Romanini (0000-0003-2301-5363), Juliana Silveira Lima de Castro (0000-0003-0280-8356), Isabela Trindade Torres (000-0002-8645-2934), Jose Andres Sanchez (0000-0002-3078-1878), Otavio Micelli Neto, (0000-0003-3803-5578) Eloy Taglieri(0000-0003-1039-793X)J José Celso Ardengh (0000-0002-5932-2499)

Authors Contributions: Serrano JPR, Ardengh JC and Jukemura J carried out the analysis and drafted the initial paper; Serrano JPR, Guaman PF and Sanchez JA contributed to the review changes and language; Romanini SG, de Castro JSL, Torres IT, Micielli O Taglieri E: contributed with data collection; all authors reviewed and approved the final paper as submitted.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read and revised according to the PRISMA 2009 Checklist.

ABSTRACT

Background and Aims: Endoscopic retrograde cholangiopancreatography (ERCP) is the primary therapeutic procedure for the treatment of diseases affecting the biliary tree and pancreatic duct. Although the therapeutic success rate of ERCP is high, the procedure can cause complications, such as acute pancreatitis (PEP), bleeding and perforation. This meta-analysis aimed to assess the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) preventing PEP follow-up (ERCP).

Materials and Methods: Databases such as MEDLINE, EMBASE and Cochrane Central Library were searched. Only randomized controlled trials (RCTs) comparing the efficacy of NSAIDs and placebo for the prevention of PEP were included. Outcomes evaluated included the incidence of PEP, severity of pancreatitis, route of administration, types, dose, and timing of administration of NSAIDs.

Results: Twenty-six RCTs were considered eligible with a total of 8143 patients analyzed. Overall, 4020 patients used NSAIDs before ERCP and 4123 did not use the drugs (control group). Ultimately, 298 cases of post-ERCP acute pancreatitis were diagnosed in the NSAID group and 484 cases in the placebo group. The risk of PEP was lower in the NSAID group risk difference (RD): -0.04; 95% confidence interval (CI): -0.07 to - 0.03; number needed to treat (NNT), 25; P <0.05. NSAID use effectively prevented mild pancreatitis compared to placebo use (2.5% vs. 4.1%; 95% CI, -0.05 to - 0.01; NNT, 33; P <0.05), but information on moderate PEP and severe could not be fully elucidated. Only rectal administration reduced the incidence of PEP with RD: -0.06 95% CI, -0.08 to -0.04; NNT, 17; P <0.05). Furthermore, only the use of diclofenac or indomethacin was effective in

preventing PEP, with a dose of 100mg and showing that it must be administered before performing ERCP.

Conclusions: Rectal administration of diclofenac and indomethacin significantly reduced the risk of developing mild PEP. Additional RCTs are needed to compare the efficacy between NSAID routes of administration in preventing PEP after ERCP.

Key words: Pancreatitis; ERCP; diclofenac; indometachin; rectal.

Core tip: The present systematic review and meta-analysis shows results regarding the use of NSAIDs reducing the incidence of PEP. This review would be the first to be held in Latin America with a large number of RCTs. The present manuscript shows how the use of diclofenac and indomethacin rectally before ERCP would reduce the incidence of mild PEP in both high, medium and low risk patients.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a useful tool in the treatment of biliopancreatic duct diseases with high technical and clinical success rates. The most common post-ERCP adverse events (AEs) are acute pancreatitis (AP), bleeding, perforation, and cholangitis [1]. AP is the most common, with an incidence between 3.5% to 9.7% and mortality from 0.1% to 0.7% [2].

Mild AP is defined as absence of organ failure and/or local and systemic complications, moderate AP as presence of transient organ failure or local or systemic complications, and severe AP as presence of persistent organ failure with or without complications. Persistent organ failure has a risk of mortality between 36% and 50% within the first phase [3]. Post-ERCP pancreatitis (PEP) is mild at 4%, moderate between 1.8% and 2.8%, and severe between 0.3% and 0.5% [4,5].

Risk factors associated with PEP are divided into patient- and procedure-related factors. Patient-related factors include sphincter of Oddi dysfunction (SOD), female gender, history of AP, and history of PEP, whereas procedure-

related factors include difficult catheterization, passage of a guidewire in the main pancreatic duct (MPD) ≥ 1 time, and pancreatic injection ≥ 1 time [2]. The search for methods that can prevent the occurrence of PEP is important to increase patient safety and reduce its incidence rate.

Studies describe preventive measures to avoid the occurrence of PEP, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and pancreatic stent implantation. Theoretically, the use of NSAIDs that inhibit cyclooxygenase 2 (COX-2) improves the acute inflammatory effects of AP and reduces its systemic sequel [6]. NSAIDs that inhibit phospholipase A2 (indomethacin and diclofenac) play a role in the early phase of inflammatory cascade in AP. Research on the use of NSAIDs to prevent PEP started in the 1980s [7]. Randomized clinical trials (RCTs) in animals have shown that indomethacin has a low mortality rate [7]. Its properties prevent papillary edema, at least theoretically decreasing the occurrence of PEP.

The authors performed a systematic review and meta-analysis to determine the effectiveness of NSAIDs in preventing PEP. The objective was to analyze the appropriate dose, route, time of administration, and the best NSAIDs to reduce the incidence of PEP.

METHOD

Protocol and registration

This systematic review and meta-analysis was carried out in accordance with the recommendations of the *Cochrane* manual, following the items in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [8]. The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, under registration number 42016049582, and approved by the ethics committee of the Moriah Hospital, São Paulo, Brazil.

Eligibility criteria and search procedure

The eligibility criteria were organized according to the international standards patient, intervention, comparison, and outcome. “Patient” (P) was

those submitted to ERCP, "intervention" (I) was administration of different types of NSAIDs described in the literature, "comparison" (C) was the administration of placebo or other similar drugs to NSAIDs, and "outcome" (O) was the main outcome of PEP. The research was carried out in different databases or virtual libraries, among which were MEDLINE/PubMed, Embase, and central Cochrane library. The dates used were from the beginning of our study in July 2016 to December 2019.

The key words used in the MEDLINE research were ERCP, NSAIDs, pancreatitis, diclofenac, and indomethacin. For other databases, we used simpler terms, such as ERCP, pancreatitis, and NSAID. All types of studies that assessed the reduction in the incidence of PEP were researched. In this systematic review and meta-analysis, we included only RCTs that studied the incidence of PEP with the use of NSAIDs.

We excluded meta-analyses, prospective nonrandomized, retrospective studies, case series, pancreatic stents studies, NSAID vs. NSAID, drugs that are not in the NSAID group, and abstracts and papers that were requested from the author without response. There was no restriction on the language and date of publication.

We included patients of any gender >18 years old who underwent ERCP for the first time and with signed informed consent. We excluded those with previous sphincterotomy, periampullary tumor, signs of evident AP, chronic pancreatitis, allergies to NSAIDs, and active and healing gastric and duodenal ulcers.

The main outcome was to assess the reduction in the overall incidence of PEP with the use of NSAIDs. We evaluated the reduction in incidence in relation to the severity of PEP (mild, moderate, and severe), types of NSAIDs (diclofenac, indomethacin, valdecoxib, ketoprofen, naproxen, and celecoxib), different routes of administration (rectal (R), oral (O), intramuscular (IM), and intravenous (IV)), and dose and time of administration (before, during, after, and before/after ERCP).

Evaluation of eligibility criteria and study selection

Two reviewers selected RCTs independently and by group analysis. Any disagreement was resolved by the reviewers and group members after consensus. The study selection process was described in the PRISMA flowchart [8]. This systematic review and meta-analysis was organized in relation to the critical assessment instruments according to the type of design of the JADAD scale [9]. Each study was classified according to the risk of bias, randomization, allocation, blinding, losses, prognostic factors, results, and patient number needed to treat (NNT).

Data analysis

Data were extracted based on the information on treatment intention. For all outcomes, risk difference (RD) was considered for analysis with a 95% confidence interval and statistical significance of $P < 0.05$. The difference between the outcomes of the analysis of each subgroup was calculated through RD together with dichotomous variables.

The analysis was performed with the statistical software RevMan 5.3 using the Mantel–Haenszel (MH) test with *fixed effect* (FE). Heterogeneity was considered by I^2, with a cutoff of 50%. When a value ≥50% was found, sensitivity analysis was performed to try to identify a study with a higher probability of publication bias ("outlier"), through graphic expression of the "funnel plot" with model or FE.

The sensitivity study aimed to identify the publication bias that justifies heterogeneity through the Egger funnel plot test. Once the publication biases were identified, which maintained heterogeneity ≥50%, it was decided to work with RD and randomized effect (RE) and work or interpret within the present systematic review and meta-analysis with a substantial or true heterogeneity.

RESULTS

Selection of studies

The evaluated articles were presented in the PRISMA flowchart with the inclusion of 26 RCTs and the exclusion of 142 articles (Fig. 1). As described, 26

RCTs were selected and evaluated [6,7,10-33] and were considered eligible to compose the study with a total of 8143 patients. The intervention group (NSAID) included 4020 patients and the comparison group (control) included 4123 patients (placebo and other substances).

Figure 1. Inclusion of 26 RCTs in the PRISMA flowchart

Study characteristics

We organized the studies after the consensus of two independent reviewers and after the group's consensus. Table 1 presents references in alphabetical order, year, country of publication, route of administration, dose, and type of NSAIDs. Out of 26 RCTs, diclofenac was used in 12 [10-21], indomethacin in 10 [7, 22-30], COX-2 inhibitors in 2 [6,31], and other NSAIDs in 2 [32,33]. Table 2 presents references in alphabetical order, type of substance used (comparison) and number (n), and time of NSAID administration.

Table 1. Characteristics of 26 RCTs. Administration route, dose, and type of NSAID

Table 2. Characteristics of 26 RCTs. Comparison group (number), administration time (before, during, after, and before/after ERCP), N = total number of patients, and number of patients intervention

Description of articles

In assessing the risk of bias, all articles have adequate randomization, allocation, and blinding. The losses did not reach 20%. The JADAD score was above 3, which was satisfactory for inclusion in all studies. The description of each article is shown in Table 3. The time for the diagnosis of PEP described in RCTs ranged from 24 to 72 hours and patients met at least two of Banks' three diagnostic criteria: history of abdominal pain, nausea, or vomiting, increase in serum amylase, and image compatible with AP.

Table 3. Description of 26 RCTs in relation to allocation, losses, blinding, prognosis, and JADAD

PEP frequency

Overall incidence and forest plot can be seen in Figure 2. In total there were 298 and 484 episodes of PEP in the intervention (4020) and comparison group (4123), respectively. RD was 95% CI −0.04 (−0.07, −0.03), $P < 0.05$, and NNT = 25.

Figure 2. *Forest plot* of global PEP incidence

Figure 3. *Funel plot* of global PEP incidence

PEP severity

Fourteen articles evaluated the incidence rate of mild PEP. In the intervention and comparison groups, we found 2600 and 2569 patients, respectively. There were 136 and 203 episodes of mild AP in the intervention (2600) and comparison group (2569), respectively. RD was 95% CI 0.03 (−0.05, −0.01), $P < 0.05$, and NNT = 33. Eleven articles evaluated the incidence of moderate PEP. In the intervention and comparison groups, 2134 and 2150 patients were allocated, respectively. There were 54 and 203 moderate PEP in the intervention and comparison group, respectively. RD was 95% CI - 0.01 (-0.02, 0.00) and $P > 0.05$. Seven articles reported the incidence of severe PEP. A total of 1740 and 1747 patients were allocated to the intervention and comparison groups, respectively. There were 16 and 23 severe PEP in the intervention and comparison group, respectively. RD was 95% CI –0.00 (−0.01, 0.00) and $P > 0.05$. The forest plot shows the severity of PEP (Fig. 3).

Figure 4. *Forest plot* of the incidence according to PEP severity

Figure 5. *Funel plot* of the incidence according to PEP severity

Administration route

Nineteen articles described the rectal route to administer NSAIDs. In the intervention and comparison groups, 3000 and 3017 patients were allocated, respectively. There were 208 and 388 PEP in the intervention and comparison group, respectively. RD was 95% CI −0.06 (−0.08, −0.03), $P < 0.05$, and NNT = 17. In three articles, IV route was described and the number of patients allocated to the intervention and comparison groups was 391 and 420 patients, respectively. There were 20 and 24 PEP in the intervention and comparison group, respectively. RD was 95% CI –0.00 (−0.04, 0.03) and $P > 0.05$. In three articles, the route of administration described was oral and the number of patients allocated to the intervention and comparison groups was 223 and 401 patients, respectively. There were 47 in the intervention and 49 PEP in the comparison group. RD was 95% CI −0.00 (−0.05, 0.04) and $P>0.05$. Two articles described IM route, with 223 and 195 patients allocated to the intervention and comparison groups, respectively. There were 23 PEP in the intervention group and 23 in the comparison group. RD was 95% CI –0.03 (−0.13, 0.07) and $P > 0.05$. The forest plot describes the different routes of administration (Fig. 4).

Figure 6. *Forest plot* of the incidence of PEP according to different routes of administration

Figure 7. *Funel plot* of the incidence of PEP according to different routes of administration

Types of NSAIDs

Diclofenac was used to prevent PEP in 15 articles. A total of 1709 and 1792 patients were allocated to the intervention and comparison groups, respectively. In the intervention and comparison group, 150 and 229 PEP occurred, respectively. RD was 95% CI –0.04 (-0.08, -0.01), $P<0.05$, and NNT = 25. Indomethacin has been described in seven articles. In the intervention and comparison groups, 1713 and 1704 patients were allocated, respectively. A total

of 109 and 197 PEP occurred in the intervention and comparison group, respectively. RD was 95% CI –0.06 (−0.09, −0.02), *P*<0.05, and NNT = 17. Two articles described the use of COX-2 inhibitors in the prevention of PEP. There were 212 patients allocated to the intervention and 212 to the comparison group. In the intervention and comparison groups, 22 PEP and 25 PEP occurred, respectively. RD was 95% CI –0.01 (−0.07, 0.05) and *P* > 0.05. Naproxen (1) and ketoprofen (1) have been described for the prevention of PEP. In the global analysis of both NSAIDs, 386 (intervention) and 415 (comparison) patients were allocated. In the intervention and comparison groups, 17 and 33 patients had PEP, respectively. RD was 95% CI –0.04 (−0.18, 0.09) and *P* > 0.05. Figure 5 shows the forest plot of the incidence of PEP using different types of NSAIDs.

Figure 8. *Forest plot* showing the incidence of PEP with different types of NSAIDs

Figure 9. *Funel plot* showing the incidence of PEP with different types of NSAIDs

Timing of NSAID administration

Thirteen articles described the use of NSAIDs before ERCP to prevent PEP. In the intervention and comparison groups, 1513 and 1585 patients were allocated, respectively. There were 115 and 229 PEP described in the intervention and comparison groups, respectively. RD was 95% CI –0.07 (−0.11, −0.03), *P* < 0. 05, and NNT = 14.

Ten articles described the use of NSAID after ERCP to prevent PEP. In the intervention and comparison groups, 1963 and 1996 patients were allocated, respectively. There were 130 and 208 PEP described in the intervention and comparison groups, respectively. RD was 95% CI –0.04 (−0.07, −0.01), *P* < 0. 05, and NNT = 25. Two articles described the use of NSAID before and after ERCP to prevent PEP. A total of 321 and 316 patients were allocated to the intervention and comparison groups, respectively. There were 37 and 36 PEP described in the intervention and comparison groups, respectively. RD was 95% CI 0.00 (−0.05, −0.05) and *P* > 0.05. Only one article described the use of NSAIDs during ERCP to prevent PEP. In the intervention and comparison groups, 223 and 226 patients were allocated, respectively. There were 16 and 11 PEP described in the

intervention and comparison groups, respectively. In this work, detailed statistical analysis was not possible. The forest plot that shows the incidence of PEP in relation to the timing of NSAID administration is in Figure 6.

Figure 10. *Forest plot* shows the incidence of PEP in relation to the timing of NSAID administration

Figure 11. *Funel plot* shows the incidence of PEP in relation to the timing of NSAID administration

DISCUSSION

The use of NSAIDs and their impact on the prevention of PEP has been described in numerous RCTs. Although the number of RCTs is small and there were no convincing results presented, the major international societies of endoscopy and gastroenterology recommend its use in daily clinical practice, but always making it clear that it is up to the endoscopist to decide whether or not to use it.

The European Society of Gastrointestinal Endoscopy recommends the use of diclofenac or indomethacin at a dose of 100 mg before ERCP in all patients whether they are at high, medium, or low risk for PEP and when there is no contraindication [2]. Japan Gastroenterological Endoscopy Society advocates a similar policy for the intrarectal administration of NSAIDs in all cases of ERCP whenever there is no contraindication [34]. The American Society for Gastrointestinal Endoscopy (ASGE) [35] recommends the administration of indomethacin in medium- and high-risk patients.

The Brazilian Society of Digestive Endoscopy (SOBED) does not define an effective method to prevent PEP. In Brazilian territory, there are books dedicated to the subject that recommend the use of indomethacin as a method of preventing PEP [36]. A systematic Brazilian review that shows statistical significance with the use of indomethacin and diclofenac stands out after analyzing 21 studies [37].

Unlike systematic reviews already published on NSAID use to reduce the risk of PEP, the current study included only RCTs, with a more robust methodology, in which an analysis was carried out in relation to the prevention

of PEP and its incidence. The global analysis according to the severity of AP episode, type of NSAID, dose, and time and route of administration shows the maturity for a more detailed perception of important details, which contributed to a more robust conclusion.

The analysis of 26 RCTs showed a significant reduction in the risk of PEP with the use of NSAIDs in both high and low risk patients. However, this study revealed that AEs most avoided by its use was in mild AP. This study shows the efficacy of indomethacin (100 mg) or diclofenac (100 mg) rectally before ERCP, with statistical significance and lower NNT compared to post-ERCP administration.

Due to the small number of RCTs published in the literature, it was not possible to identify whether another route of administration (oral, IV, and IM), another type of NSAID, another time of administration, and doses lower or greater than 100mg are effective in preventing PEP. This finding brings to light the need for more large multicenter RCTs comparing other NSAIDs, other routes, and times and doses of administration so that better work and/or systematic reviews and meta-analysis with more robust methodology can exist. However, the decision may be influenced by cost, as indomethacin is more expensive than diclofenac. A cost comparison of the types of NSAIDs to decrease the incidence of PEP should be conducted, in order to obtain more data in this regard. As far as is known, this is the first meta-analysis on the prevention of PEP with the use of NSAIDs, which includes all types of NSAIDs described so far in the literature, such as diclofenac, indomethacin, naproxen, valdecoxib, celecoxib, and ketoprofen.

COX-2 inhibitor, regardless of the initial trigger (the injured pancreatic acinar cell), quickly leads to a pro-inflammatory cascade with a short therapeutic intervention window for some type of intervention. Cyclooxygenase (COX) enzymes play an important pro-inflammatory role in AP. The isoform of COX-2 is overexpressed in AP, while the expression of COX-1 remains constant. Pharmacological inhibition of COX-2 improves the severity of acute effects on AP

and its systemic and ischemic sequelae. COX-2 could show some benefit over AP [6].

Diclofenac and indomethacin, by inhibiting phospholipase A2, play a role in the early phase of inflammatory cascade in AP. Phospholipase A2 inhibition results in the suppression of several important classes of pro-inflammatory lipids (prostaglandins, leukotrienes, and platelet-activating factor). NSAIDs further inhibit neutrophil-endothelial cell binding. Among all NSAIDs studied in RCTs in animals, indomethacin showed a lower mortality rate [7]. However, the effectiveness of other NSAIDs must be investigated.

It is important to emphasize that the results of this meta-analysis may have been influenced by heterogeneity > 50%, in relation to the weight of each RCT included in this study. When we refer to the weight of each study, we refer to the number of patients in each of them which was observed within the forest plot with a minimum weight of 1.5% [26] and a maximum weight of 6.3% [34]. These weights influence the time to be interpreted in the RevMan 5.3 software.

As mentioned by ESGE, there are different demographic factors with respect to who can develop PEP, such as patients with suspected SOD, female, previous AP, previous PEP, difficult cannulation, guidewire passages and MPD contrast, child, fine bile duct, absence of chronic pancreatitis, normal serum bilirubin, end-stage renal disease, previous sphincterotomy, pancreatic sphincterotomy, balloon sphincteroplasty, and failure to remove bile duct stones [38]. For these reasons, PEP prevention is important to increase patient safety.

This study emphasized how each RCT reached the diagnosis of AP, which each of the authors defined the episode of AP with the presence of abdominal pain after 24 to 72 hours of ERCP, increased pancreatic enzymes, and an image compatible with inflammatory alteration of the pancreatic gland [6.8, 11-34]. The recent ESGE guideline suggests testing serum amylase and/or lipase 2 to 6 hours after ERCP in patients with post-ERCP abdominal pain who should be discharged on the same day of ERCP. Patients with serum amylase and lipase values below 1.5 to 4 times the normal limit can be discharged without concern

for PEP development [2]. Another limitation of the study was that not all RCTs stratified the severity of AP in order to be able to adequately interpret at what level of severity the use of NSAIDs may be most beneficial.

Of all 26 RCTs, 521 episodes of AP were assessed for severity. In 339, the AP episode was mild, representing 65% of stratified patients (339/521). Thus, our results demonstrated that the use of NSAIDs prevents the development of mild PEP. Finally, this systematic review focused solely and exclusively on PEP and its severity, but it is important to note that other AEs can occur post-ERCP that this review did not include.

Thus, in relation to the subgroups examined, the rectal route adequately reduces the incidence of PEP. The use of NSAIDs was shown to be better in mild AP episodes. Both diclofenac and indomethacin were effective in preventing PEP. The best time to apply is before ERCP and the most appropriate dose that revealed the best results was 100mg.

Other RCTs are needed to resolve some remaining doubts, as follows: Would other NSAIDs be more effective? Would the IV route be not better? Could smaller doses of more potent NSAIDs be more effective in preventing PEP?

Therefore, it is concluded that rectal administration of 100-mg diclofenac or 100-mg indomethacin before ERCP prevents the occurrence of mild episodes of PEP.

ARTICLE HIGHLIGHTS

Research background:

ERCP is one of the most used and performed therapeutic procedures when referred to the bile ducts access. We have to understand that important complications can appear as: PEP, bleeding, puncture and cholangitis. PEP is considered the main complication after the procedure. Large societies such as ASGE, ESGE and, Japanese describe it as a very important complication and methods must be used to prevent and reduce this pathology. Various methods such as using NSAIDs, prostheses, somastostatin and others were used but NSAIDs showed a higher rate of effectiveness.

Research motivation:

In many studies, NSAIDs have demostrated good results, but, on the other hand, it also has conflicting results. As there is still a controversy as to whether the use of NSAIDs would help in the reduction of PEP, our group opted to carry out the present manuscript with all the RCTs described in the literature and show results that can help in its use as a prevention method in PEP.

Research objectives:

Our main objective was to analyze the effectiveness of NSAIDs versus "Placebo" as a method of choice or first line to reduce PEP, obtaining the best and most recent RCTs. In the field section of discussion, our objectives and results were mentioned as a therapeutic emphasis when using all NSAIDs available in the literature, their route of administration and when it should be used. At the same time, we also hope that our research can play an important role within the scientific medical community.

Research methods:

We performed this meta-analysis according to the Preferred reporting items guidelines for systematic review and meta-analysis. Virtual databases were used as main data until December 2019. The research results were directed to be carried out only with RCTs without date or language restriction. Once the studies were selected, they were organized according to the PICO criteria and the design scale was behind the JADAD scale. The statistical analysis was performed using RevMan 5.3 software. As recommended, the main point to be evaluated was the reduction in the incidence of PEP. Subgroup analysis was also done: severity of pancreatitis, route of administration, time of administration and the different types of NSAIDs described in the literature. The results were evaluated using the Higgins test method, using a risk difference with a random effect with a significance of $p < 0.05$, 95% CI and interpreted as true heterogeneity.

Research results:

In the present manuscript with 26 high quality RCTs, interpreting the use of NSAIDs vs Placebo as a method of reducing PEP, we observed a total of 8143 patients. 4020 patients used NSAIDs before ERCP and 4123 did not use the drugs (control group). Finally, 298 cases of acute pancreatitis after ERCP were diagnosed in the NSAID group and 484 cases in the placebo group. The risk of PEP was lower in the risk difference (RD) of the NSAID group: -0.04; 95% confidence interval (CI): -0.07 to - 0.02; number needed to treat (NNT), 25; P <0.05. The use of NSAIDs effectively prevented mild pancreatitis compared to the use of placebo (2.5% vs. 4.1%; 95% CI, -0.05 to -0.01; NNT, 33; P <0.05) , but information on moderate and severe PEP could not be fully demonstrated. Only rectal administration reduced the incidence of PEP with DR: -0.06 95% CI, -0.08 to -0.04; NNT, 17; P <0.05).

Research conclusions

The conclusion in the present manuscript shows that the use of NSAIDs does help in reducing the incidence of PEP. In particular it helps in the reduction of mild acute pancreatitis. The drugs that showed the best effectiveness were diclofenac and indomethacin. The best route of administration to be applied would be rectally and the best time for its administration was before ERCP.

Research perspectives

Our manuscript takes into account all RCTs and is an effort far beyond expectations. Our prospects are that the scientific community, read carefully, and know how to decide the best conduct with an effective method in reducing PEP.

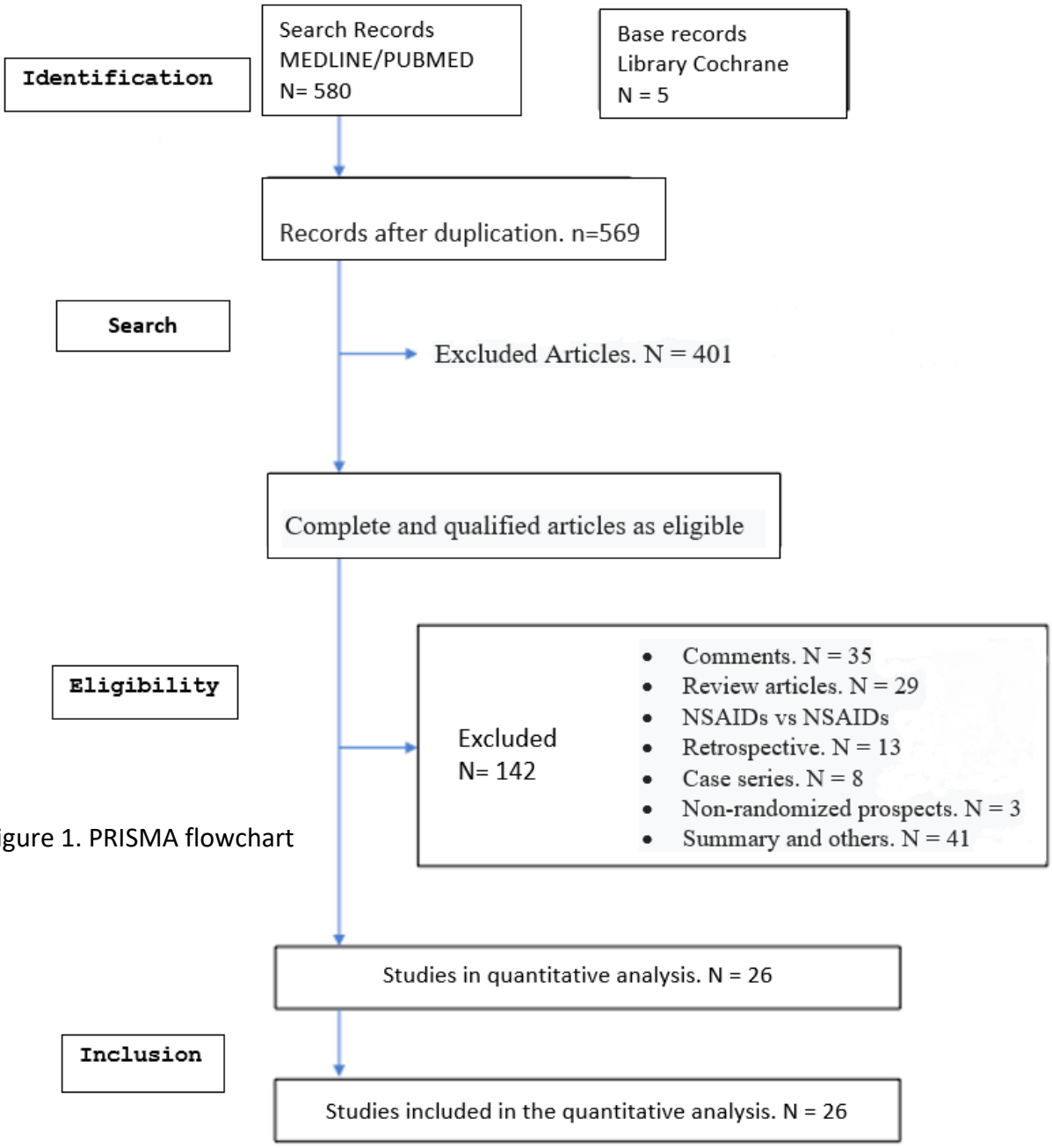

Figure 1. PRISMA flowchart

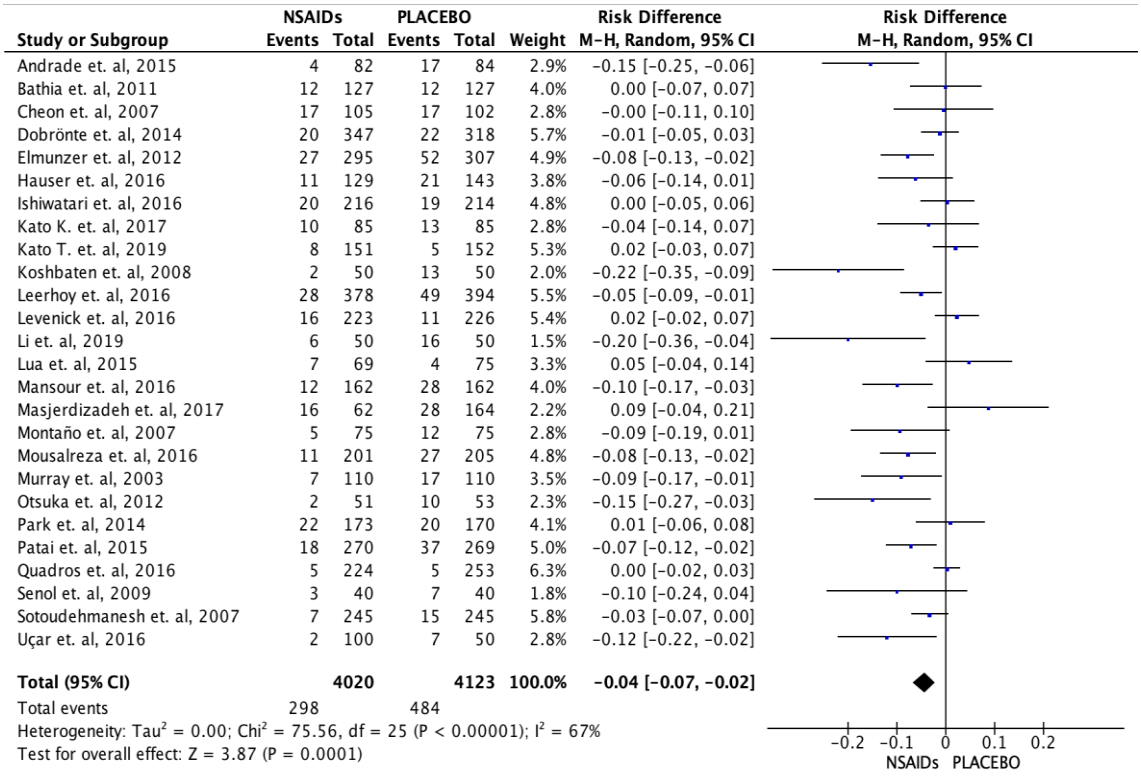

Figure 2. *Forrest plot* of global PEP incidence

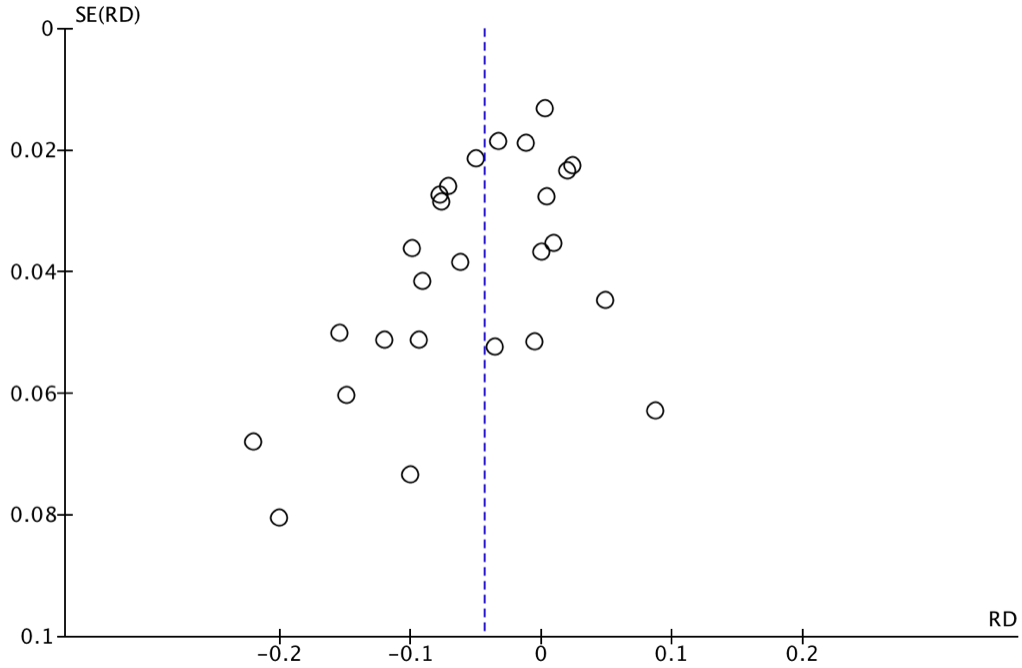

Figure 3. *Funel plot* of global PEP incidence

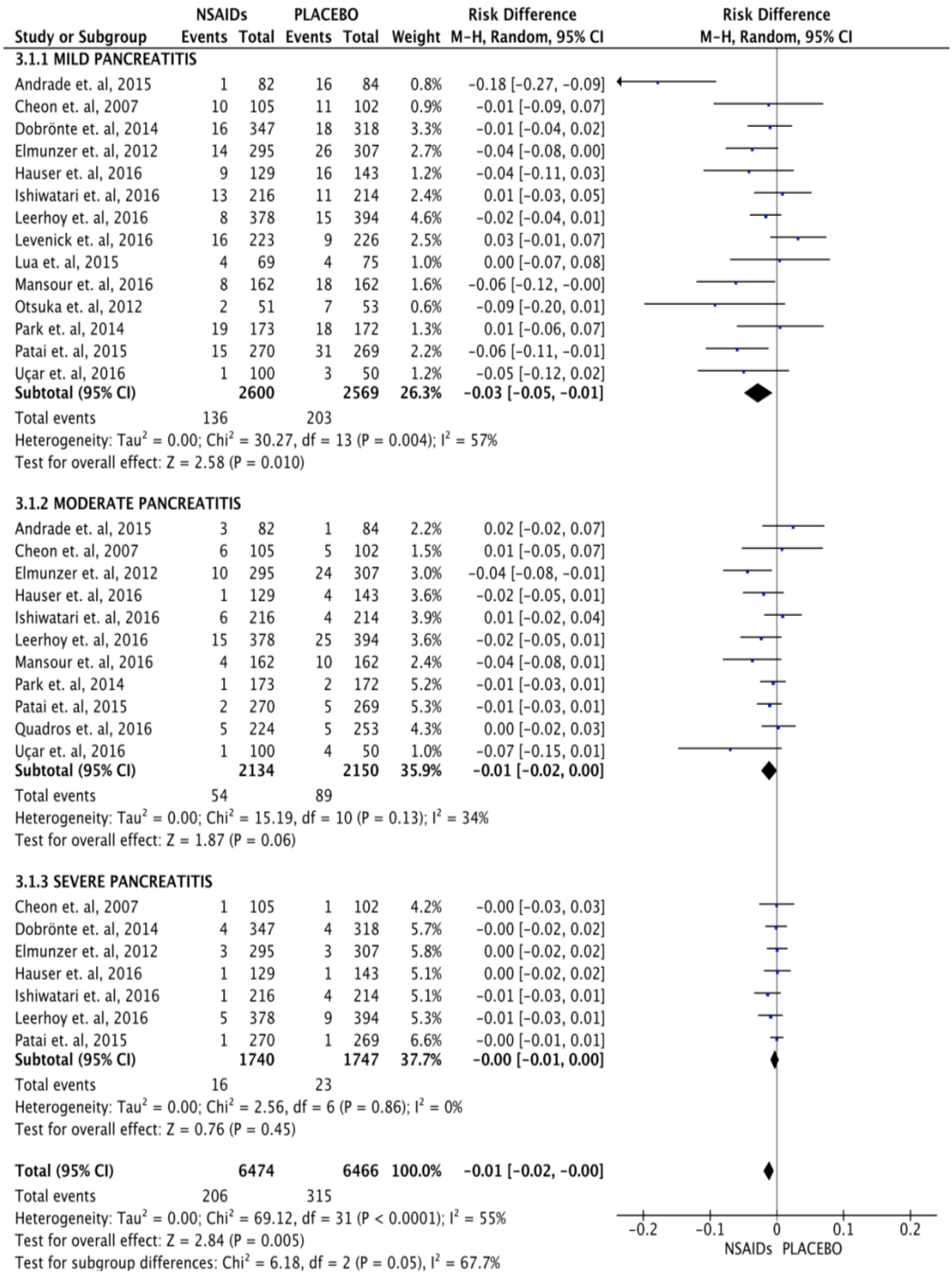

Figure 4. *Forrest plot* of the incidence according to PEP severity

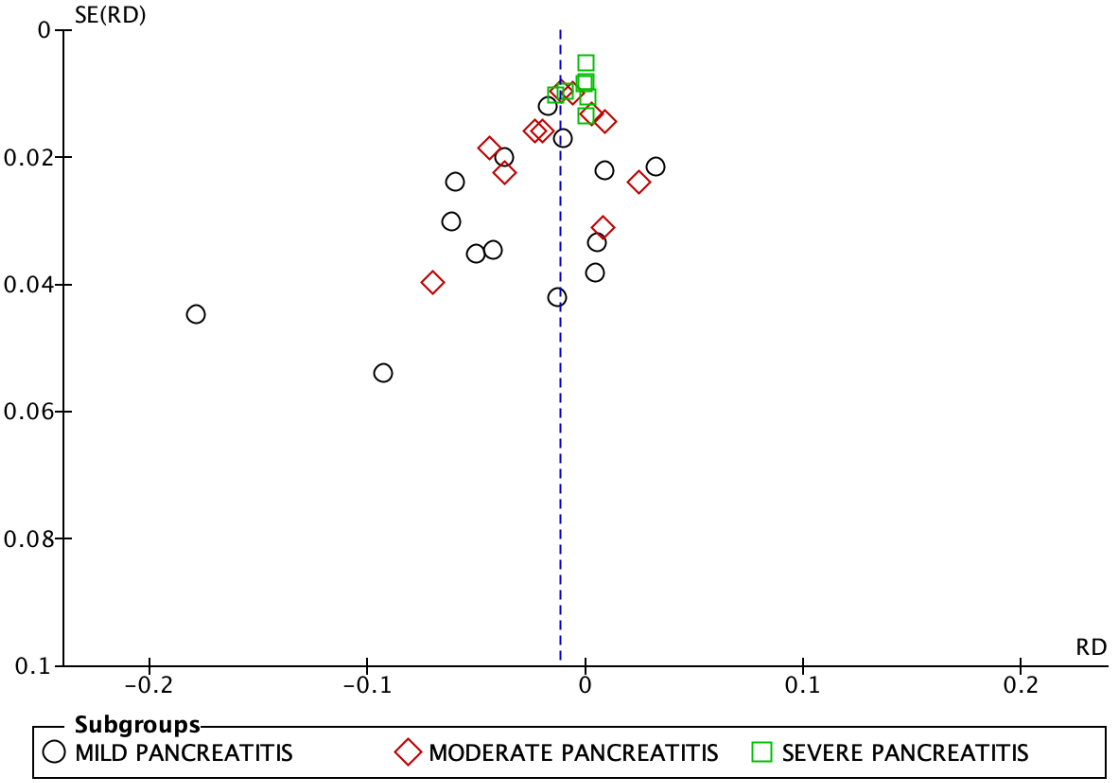

Figure 5. *Forrest plot* of the incidence according to PEP severity

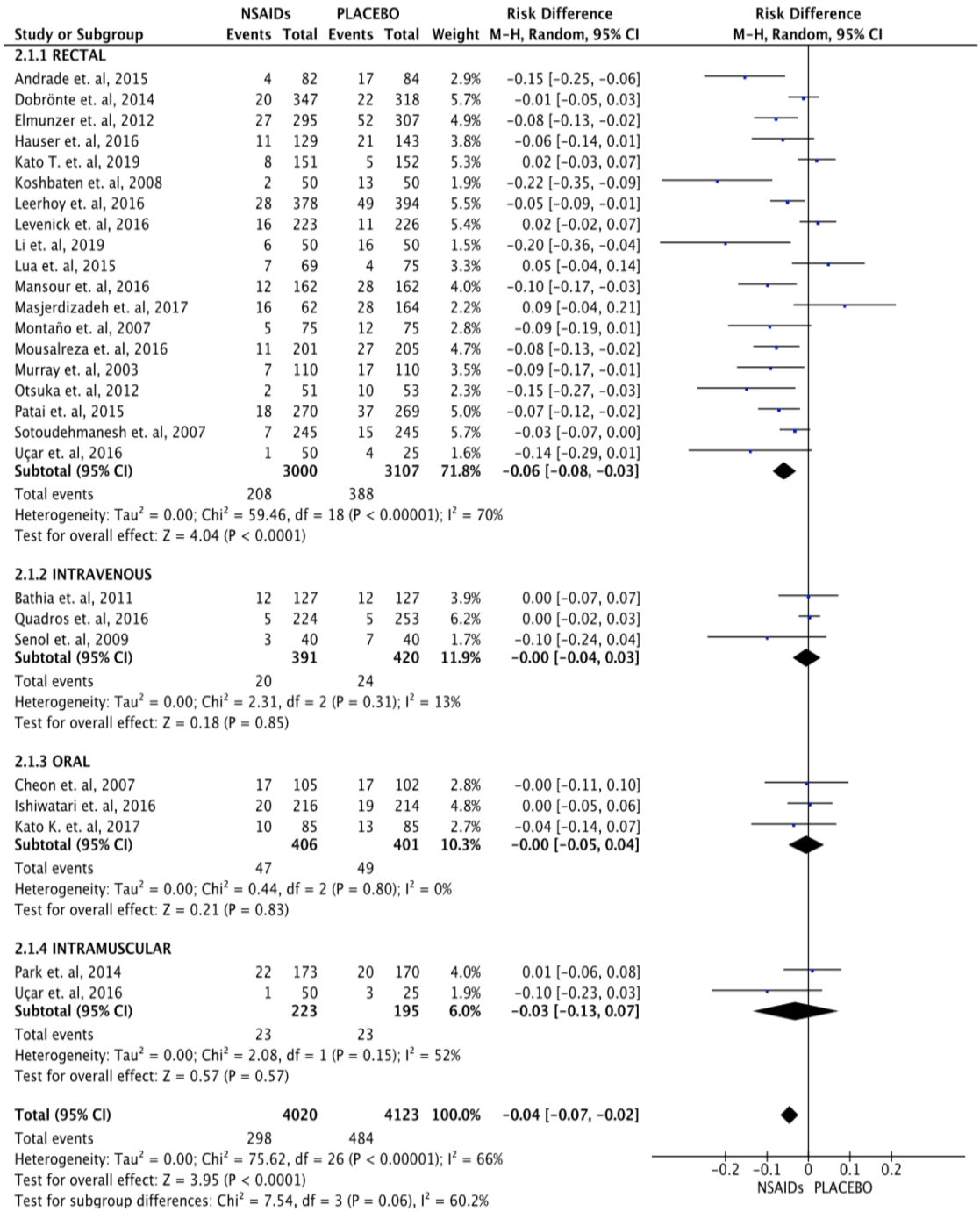

Figure 6. *Forrest plot* of the incidence of PEP according to different routes of administration

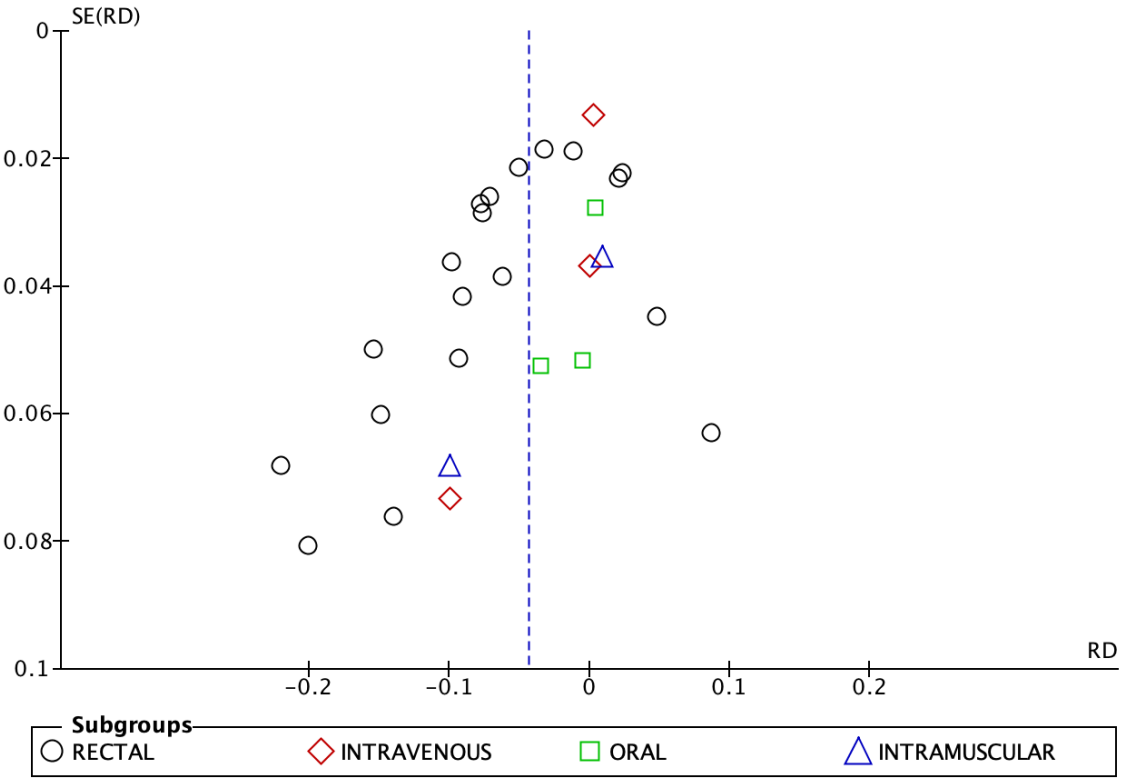

Figure 7. *Funel plot* of the incidence of PEP according to different routes of administration

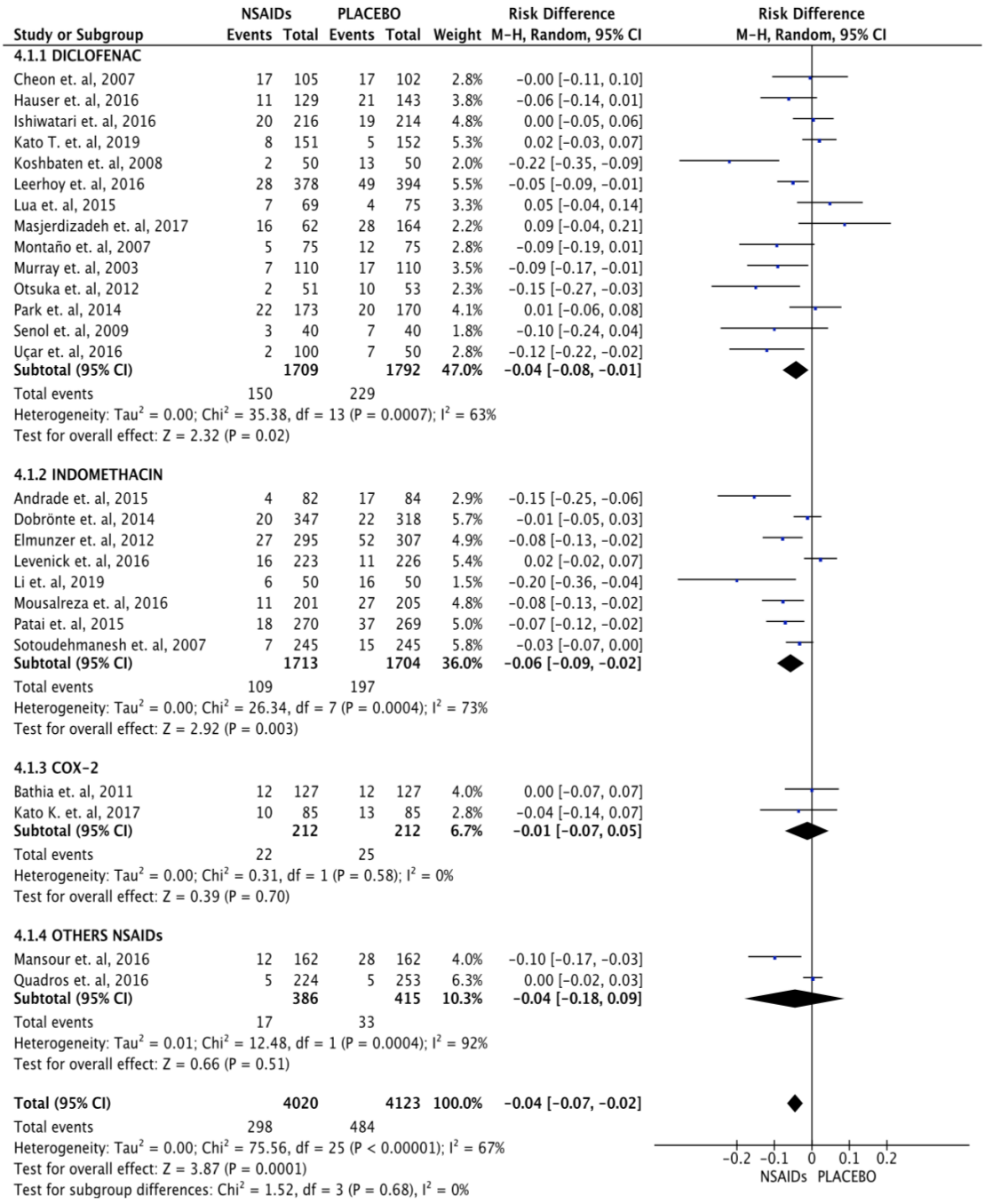

Figure 8. *Forest plot* showing the incidence of PEP with different types of NSAIDs

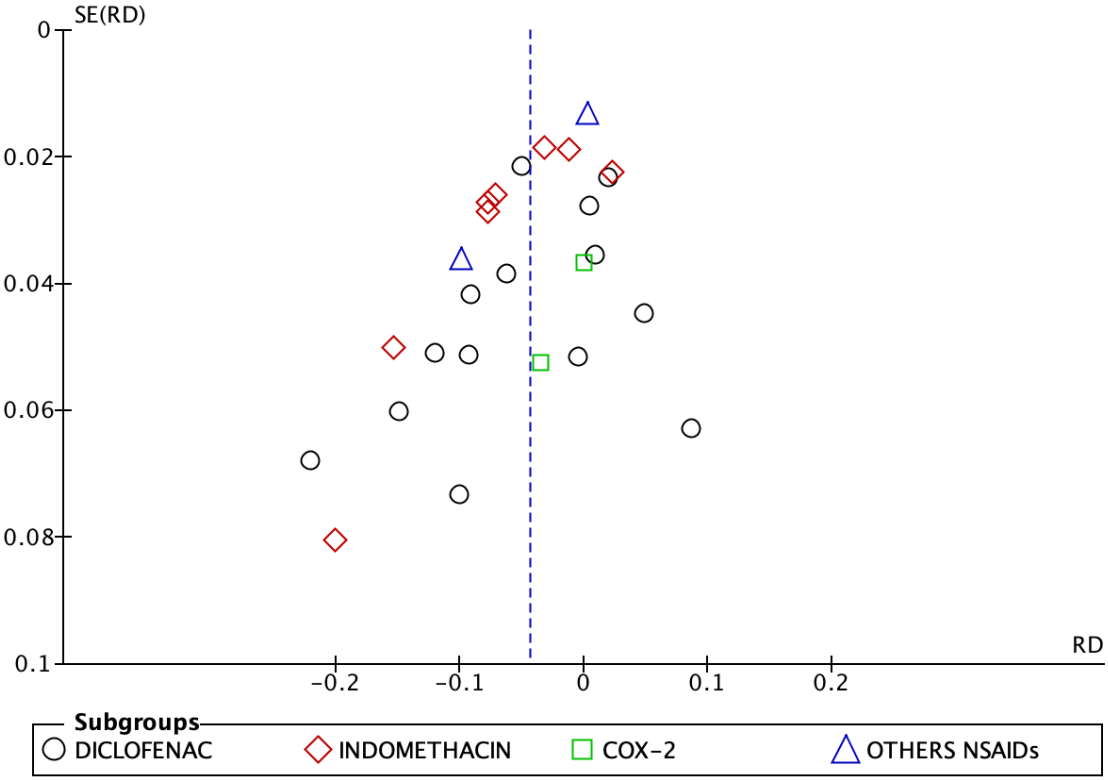

Figure 9. *Funel plot* showing the incidence of PEP with different types of NSAIDs

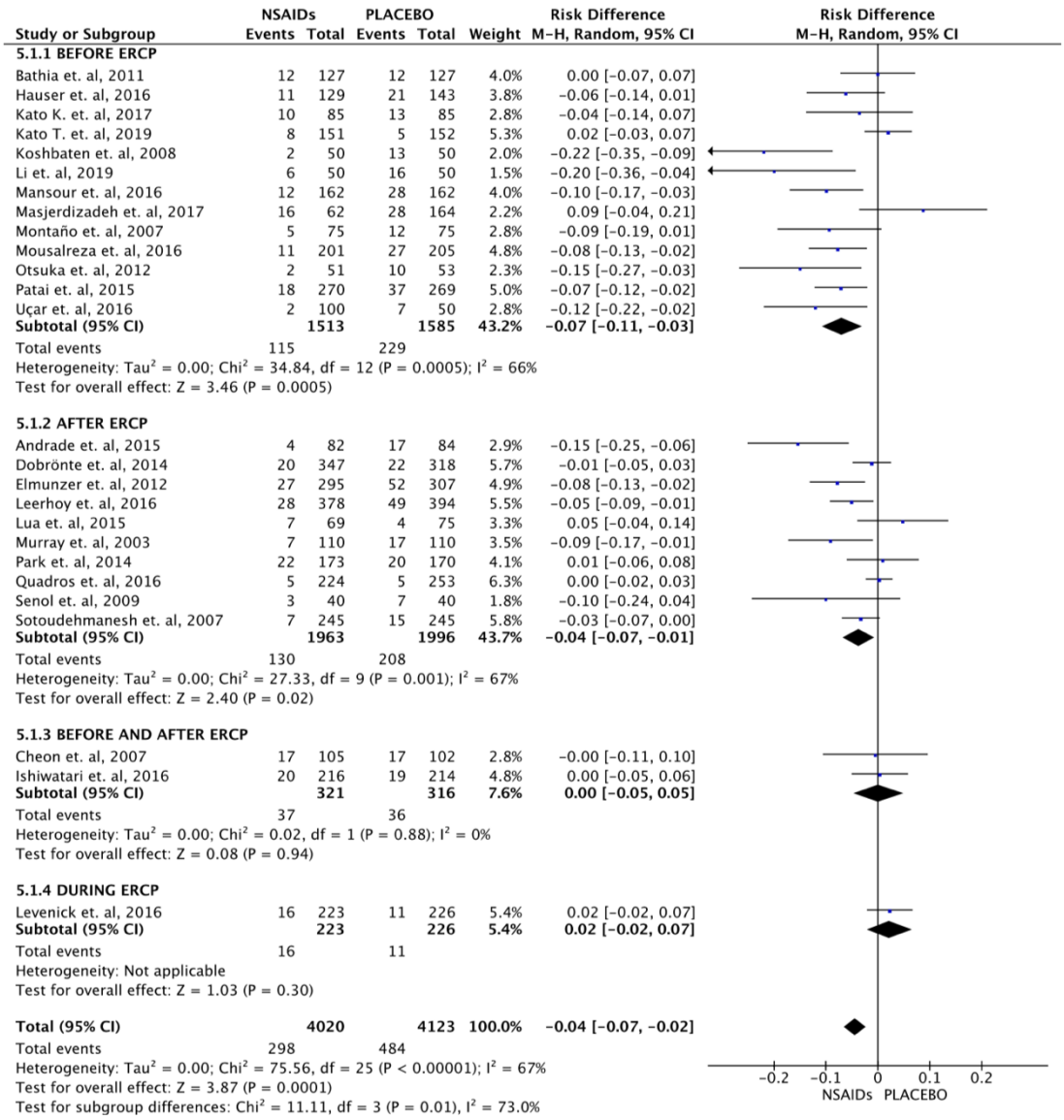

Figure 10. *Forest plot* showing the incidence of PEP in relation to timing of NSAID administration

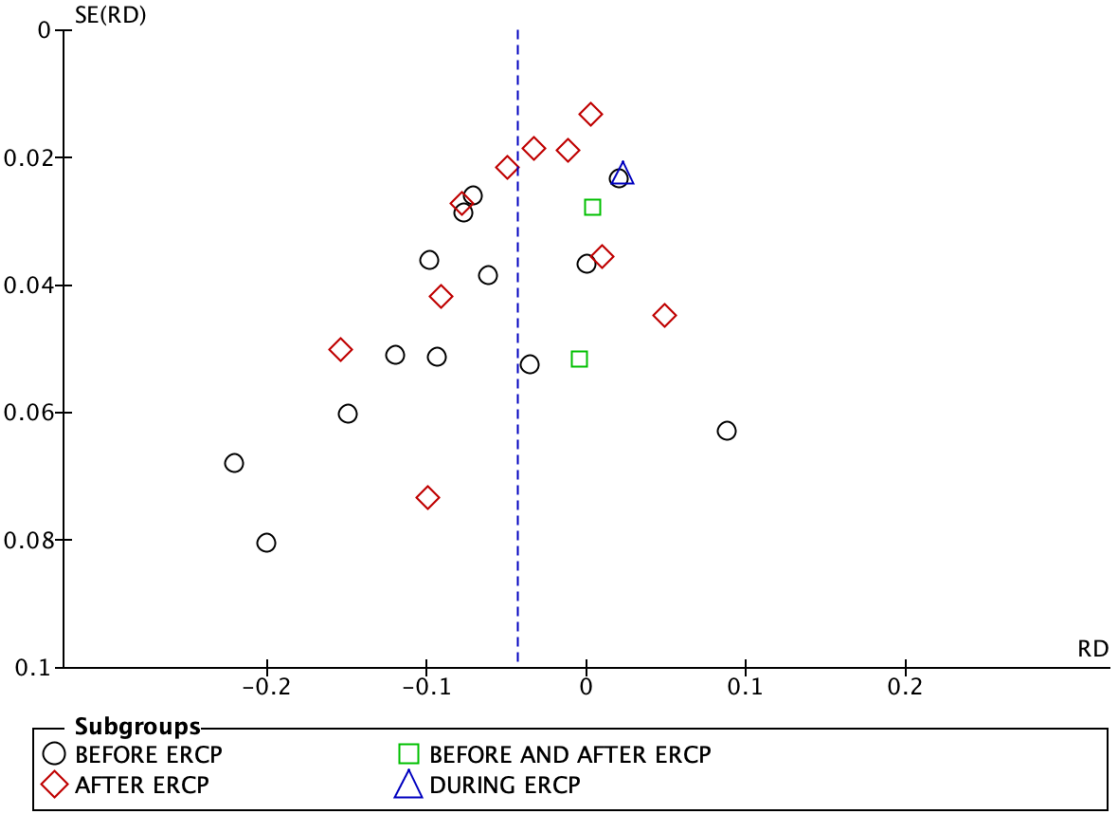

Figure 11. *Funel plot* showing the incidence of PEP in relation to timing of NSAID administration

Reference	Year	Country	Route	Dose	NSAID type
Andrade et al., 2015	2015	México	R	100 mg	Indomethacin
Bathia et al., 2011	2011	India	IV	20 mg	Valdecoxib
Cheon et al., 2007	2007	USA	O	50 mg	Diclofenac
Dobrönte et al., 2014	2014	Hungary	R	100 mg	Indomethacin
Elmunzer et al., 2012	2012	USA	R	100 mg	Indomethacin
Hauser et al., 2016	2016	Croatia	R	100 mg	Diclofenac
Ishiwatari et al., 2016	2016	Japan	O	100 mg	Diclofenac
Kato K. et al., 2017	2017	Japan	O	400 mg	Celecoxib
Kato T. et al., 2019	2019	Japan	R	25/50mg	Diclofenac
Koshbaten et al., 2008	2008	Iran	R	50 mg	Diclofenac
Leerhoy et al., 2016	2016	Dinmark	R	100 mg	Diclofenac
Levenick et al., 2016	2016	USA	R	100 mg	Indomethacin
Li et al., 2019	2019	China	R	100 mg	Indomethacin
Lua et al., 2015	2015	Malasya	R	100 mg	Diclofenac
Mansour et al., 2016	2016	Iran	R	500 mg	Naproxen
Masjerdizadeh et al., 2017	2017	Iran	R	50 mg	Indomethacin
Montaño et al., 2007	2007	México	R	100 mg	Indomethacin
Mousalreza et al., 2016	2016	Iran	R	100 mg	Indomethacin
Murray et al., 2003	2003	Scotland	R	100 mg	Diclofenac
Otsuka et al., 2012	2012	Japan	R	50 mg	Diclofenac
Park et al., 2014	2014	Korea	IM	100 mg	Diclofenac
Patai et al., 2015	2015	Hungary	R	100 mg	Indomethacin
Quadros et al., 2016	2016	Brazil	IV	100 mg	Cetoprofen
Senol et al., 2009	2009	USA	IV	50 mg	Diclofenac
Sotoudehmanesh et al., 2007	2007	Iran	R	100 mg	Indomethacin
Uçar et al., 2016	2016	Turkey	IM and IV	75/100 mg	Diclofenac

R, rectal; *IV*, intravenous; *O*, oral; *IM*, intramuscular

Table 1. Characteristics of 26 RCTs. Administration route, dose, and type of NSAID

Reference	Comparison (n)	Administration time (after, before, and during)	N	Intervention
Andrade et al., 2015	Glycerin (84)	Before ERCP	166	82
Bathia et al., 2011	Parche Nitrodermico (127)	Before ERCP	254	127
Cheon et al., 2007	Placebo SN (102)	Before and after ERCP	207	105
Dobrönte et al., 2014	Placebo SN (318)	After ERCP	665	347
Elmunzer et al., 2012	Placebo SN (307)	After ERCP	602	295
Hauser et al., 2016	Ceftazidime (143)	Before ERCP	272	129
Ishiwatari et al., 2016	Placebo SN (214)	Before and after ERCP	430	216
Kato K. et al., 2017	Saline solution(85)	Before ERCP	170	85
Kato T. et al., 2019	None (152)	Before ERCP	303	151
Koshbaten et al., 2008	Placebo SN (50)	Before ERCP	100	50
Leerhoy et al., 2016	None (394)	After ERCP	772	378
Levenick et al., 2016	Placebo SN (226)	During ERCP	449	223
Li et al., 2019	Glycerin (50)	Before ERCP	100	50
Lua et al., 2015	None (75)	After ERCP	144	69
Mansour et al., 2016	Placebo SN (162)	Before ERCP	324	162
Masjerdizadeh et al., 2017	Placebo lactated Ringer's solution (124)	Before ERCP	186	62
Montaño et al., 2007	Glycerin (75)	Before ERCP	150	75
Mousalreza et al., 2016	Saline solution(205)	Before ERCP	406	201
Murray et al., 2003	Placebo SN (110)	After ERCP	220	110
Otsuka et al., 2012	Saline solution(53)	Before ERCP	104	51
Park et al., 2014	Saline solution(170)	After ERCP	343	173
Patai et al., 2015	Placebo SN (269)	Before ERCP	539	270
Quadros et al., 2016	Saline solution(253)	After ERCP	477	224
Senol et al., 2009	Placebo SN (40)	After ERCP	80	40
Sotoudehmanesh et al., 2007	Placebo SN (245)	After ERCP	490	245
Uçar et al., 2016	None (50)	Before ERCP	150	100
Total	---	----	8103	4020

N, number; *ERCP*, endoscopic retrograde cholangiopancreatography

Table 2. Characteristics of 26 RCTs. Comparison group (number), administration time (after, before, and during ERCP), N = total number of patients, and number of patients with intervention

Reference	Randomization	Allocation	Blinding	Losses	Prognosis	AIT	JADAD
Andrade et al., 2015	Yes	Yes	No	No	Homogeneous	Yes	3
Bathia et al., 2011	Yes	Yes	No	No	Homogeneous	No	3
Cheon et al., 2007	Yes	Yes	Yes	Yes	Homogeneous	No	5
Dobrönte et al., 2014	Yes	No	No	Yes	Homogeneous	No	3
Elmunzer et al., 2012	Yes	Yes	Yes	No	Homogeneous	Yes	5
Hauser et al., 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Ishiwatari et al., 2016	Yes	Yes	Yes	Yes	Homogeneous	No	3
Kato K. et al., 2017	Yes	Yes	Yes	No	Homogeneous	Yes	4
Kato T. et al., 2019	Yes	Yes	Yes	Yes	Homogeneous	No	5
Koshbaten et al., 2008	Yes	Yes	Yes	No	Homogeneous	No	5
Leerhoy et al., 2016	Yes	No	No	No	Homogeneous	No	3
Levenick et al., 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Li et al., 2019	Yes	Yes	Yes	Yes	Homogeneous	No	5
Lua et al., 2015	Yes	Yes	No	Yes	Homogeneous	Yes	3
Mansour et al., 2016	Yes	Yes	Yes	No	Homogeneous	Yes	4
Masjerdizadeh et al., 2017	Yes	No	Yes	No	Homogeneous	Yes	4
Montaño et al., 2007	Yes	No	Yes	No	Homogeneous	No	3
Mousalreza et al., 2016	Yes	Yes	Yes	No	Homogeneous	No	3
Murray et al., 2003	Yes	Yes	Yes	No	Homogeneous	No	3
Otsuka et al., 2012	Yes	No	No	No	Homogeneous	Yes	3
Park et al., 2014	Yes	Yes	Yes	No	Homogeneous	No	3
Patai et al., 2015	Yes	Yes	Yes	Yes	Homogeneous	Yes	5
Quadros et al., 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Senol et al., 2009	Yes	No	No	No	Homogeneous	No	3
Sotoudehmanesh et al., 2007	Yes	Yes	Yes	No	Homogeneous	Yes	4
Uçar et al., 2016	Yes	No	No	Yes	Homogeneous	No	3

Table 3. Description of 26 RCTs in relation to allocation, losses, blinding, prognosis, and JADAD

REFERENCES

1. **Muhammad S Sajid**, Amir H Khawaja, Mazin Sayegh, Krishna K Singh, Zinu Philipose. 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 Dec 25; **7(19):** 1341–1349. Published online 2015 Dec 25. DOI: 10.4253/wjge.v7.i19.1341 PMCID: PMC4689797

2. **Dumonceau JM,** Kapral C, Aabakken L, Papanikolaou IS, Tringali A, Vanbiervliet G, Beyna T, Ribeiro MD, Hritz I, Mariani A, Paspatis G, Radaelli F, Lakhtakia S, Veitch AM, Van Hooft JE. ERCP-related Adverse Events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy.* 2020 Feb;**52(2):**127-149. DOI: 10.1055/a-1075-4080. Epub 2019 Dec 20. PMID: 31863440

3. **Banks PA,** Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. . 2013 Jan;**62(1**):102-11. DOI: 10.1136/gutjnl-2012-302779. Epub 2012 Oct 25. PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779

4. **Freeman M L**, DiSario J A, Nelson D B, Fennerty M B, Lee J G, Bjorkman D J, Overby C S, Aas J, Ryan M E, Bochna G S, Shaw M J, Snady H W, Erickson R V, Moore J P, Roel J P. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc. 2001 Oct;**54(4):**425-34. doi: 10.1067/mge.2001.117550.

PMID: 11577302 DOI: 10.1067/mge.2001.117550

5. **Vandervoort J,** Soetikno RM, Tham TCK, Wong RCK, Ferrari AP, Montes H, Roston AD, Slivka A, Lichtenstein DR, Ruymann FW, Dam JV, HughesM, Carr-Locke DL. Risk factors for complications after performance of ERCP. Gastrointest

Endosc. 2002;56:652–656. Gastrointest Endosc. 2002 Nov;**56(5):**652-6. PMID: 12397271 DOI: 10.1067/mge.2002.129086

6. **Bhatia V**, Ahuja V, Acharya S K, Garg PK. A randomized controlled trial of valdecoxib and glyceryl trinitrate for the prevention of post-ERCP pancreatitis. J Clin Gastroenterol. 2011 Feb;**45(2**):170-6. PMID: 20717044 DOI: 10.1097/MCG.0b013e3181eb600e

7. **Döbrönte Z**, Szepes Z, Izbéki F, Gervain J, Lakatos L, Pécsi G, Ihász M, Lakner L, Toldy E, Czakó L. Is rectal indomethacin effective in preventing of post-endoscopic retrograde cholangiopancreatography pancreatitis? World J Gastroenterol. 2014 Aug 7; **20(29):** 10151–10157. Published online 2014 Aug 7. DOI: 10.3748/wjg.v20.i29.10151 PMCID: PMC4123345

8. **Moher D,** Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement PLoS Guideline PLoS Med. 2009 Jul 21;**6(7):** e1000097. Epub 2009 Jul 21. PMID: 19621072 PMCID: PMC2707599 DOI: 10.1371/journal.pmed.1000097

9. **Jadad A R**, Moore R A, Carroll D Jenkinson C, Reynolds DJ, Gavaghan DJ , McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;**17(1):**1-12. PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4

10. **Cheon Y K,** Cho K B, Watkins J L, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc. 2007 Dec;**66(6):**1126-32. PMID: 18061712 DOI: 10.1016/j.gie.2007.04.012

11. **Hauser G**, Blažević I, Salkić N, Poropat G, Giljača V, Bulić Z, Štimac D. Diclofenac sodium versus ceftazidime for preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a prospective, randomized, controlled trial. Surg Endosc. 2017 Feb;**31(2):**602-610. PMID: 27317032 DOI: 10.1007/s00464-016-5004-9

12. **Ishiwatari H,** Urata T, Yasuda I, Matsusaki S, Hisai H, Kawakami H, Ono M, Iwashita T, Doi S, Kawakubo K, Hayashi T, Sonoda T, Sakamoto N, Kato J. No benefit of oral diclofenac on post-endoscopic retrograde cholangiopancreatography pancreatitis. Dig Dis Sci. 2016 Nov;**61(11):**3292-3301. PMID: 27447477 DOI: 10.1007/s10620-016-4251-x

13. **Katoh T,** Kawashima K, Fukuba N, Masuda S, Kobatake H, Masaki K, Araki Y, Kawano K, Nishi K, Takenaka M, Ishihara S, Kinoshita Y. Low-dose rectal diclofenac does not prevent post-ERCP pancreatitis in low- or high-risk patients. J Gastroenterol Hepatol. 2019 Dec **1**. PMID: 31788849 DOI: 10.1111/jgh.14948

14. **Khoshbaten M**, Khorram H, Madad L, Ardakani MJE, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 2008;23:e11–16. Trial J Gastroenterol Hepatol. 2008 Jul;**23**(7Pt2):e11-6. PMID: 17683501 DOI: 10.1111/j.1440-1746.2007.05096.x

15. **Leerhøy B,** Nordholm-Carstensen A, Novovic S, Mark Berner Hansen MB, Jørgensen LN. Effect of body weight on fixed dose of diclofenac for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Scand J Gastroenterol. 2016;51:1007–1012. 2016 Aug;**51(8):**1007-12. PMID: 27160512 DOI: 10.3109/00365521.2016.1172338

16. **Lua G W,** Muthukaruppan R, Menon J. Can rectal diclofenac prevent post endoscopic retrograde cholangiopancreatography pancreatitis? Dig Dis Sci. 2015;60:3118–3123. 2015 Oct;**60(10):**3118-23. PMID: 25757446 DOI: 10.1007/s10620-015-3609-9

17. **Murray B,** Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology. 2003 Jun;**124(7):**1786-91. PMID: 12806612 DOI: 10.1016/s0016-5085(03)00384-6

18. **Otsuka T,** Kawazoe S, Nakashita S, Kamachi S, Oeda S, Sumida C, Akiyama T, Ario K, Fujimoto M, Tabuchi M, Noda T. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography

pancreatitis: a randomized controlled trial. J Gastroenterol. 2012;**47**:912–917. M PMID: 22350703 DOI: 10.1007/s00535-012-0554-7

19. **Senol A,** Saritas U, Demirkan H. Efficacy of intramuscular diclofenac and fluid replacement in prevention of post-ERCP pancreatitis. World J Gastroenterol. 2009 Aug 28; **15(32):** 3999–4004. Published online 2009 Aug 28. doi: 10.3748/wjg.15.3999 PMCID: PMC2731949

20. **Uçar R,** Biyik M, Uçar E, Polat I, Çifçi S, Ataseven H, Demir A. Rectal or intramuscular diclofenac reduces the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography. Turk J Med Sci. 2016;**46:**1059–1063. PMID: 27513404 DOI: 10.3906/sag-1502-104

21. **Park S W**, Chung M J, Oh T G, Park JY, Bang B, Park SW, Song SY. Intramuscular diclofenac for the prevention of post-ERCP pancreatitis: a randomized trial. Endoscopy. 2015;47:33–39. Randomized Controlled Trial Endoscopy. 2015 Jan;**47(1):**33-9. PMID: 25409167 DOI: 10.1055/s-0034-1390743

22. **Masjedizadeh A,** Fathizadeh P, Aghamohamadi N et al. Comparative effectiveness of aggressive intravenous fluid resuscitation with lactated Ringer's solution and rectal indomethacin therapy in the prevention of pancreatitis after endoscopic retrograde cholangiopancreatography: a double blind randomised controlled clinical trial. Prz Gastroenterol. 2017;**12(4):**271-276. PMID: 29358996 PMCID: PMC5771451 DOI: 10.5114/pg.2017.72102

23. **Montaño Loza A,** Rodríguez Lomelí X, García Correa J E, Cobián CD, Guevara GC, Muñoz FM, Orozco CF, Ojeda AG. Effect of the administration of rectal indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes. Rev Esp Enferm Dig. 2007 Jun;**99(6):**330-6. PMID: 17883296 DOI: 10.4321/s1130-01082007000600005

24. **Andrade-Dávila V F,** Chávez-Tostado M, Dávalos-Cobián C, Correa JG, Loza AM, Orozco CF, Amezcua MDM, Rentería JG, Félix JR, Lares JAC, González GA, Flores AOC, Villaseñor ASA, Ojeda AG. Rectal indomethacin versus placebo to reduce the incidence of pancreatitis after endoscopic retrograde

cholangiopancreatography: results of a controlled clinical trial. BMC Gastroenterol. 2015;**15**:85. PMID: 26195123 PMCID: PMC4508969 DOI: 10.1186/s12876-015-0314-2

25. **Elmunzer B J,** Scheiman J M, Lehman G, Chak A, Mosler P, Higgins PDR, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SH, Nicholson S, Fogel EL .U.S. Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;**366**:1414–1422. PMID: 22494121 PMCID: PMC3339271 DOI: 10.1056/NEJMoa1111103

26. **Levenick J M**, Gordon S R, Fadden L L, Levy LC, Rockacy MJ, Hyder SM, Lacy BE, Bensen SP, Parr DD, Gardner TB. Rectal indomethacin does not prevent post-ercp pancreatitis in consecutive patients. Gastroenterology 2016150911–917.; quiz **e19**. PMID: 26775631 PMCID: PMC4808426 DOI: 10.1053/j.gastro.2015.12.040

27. **Li L**, Liu M, Zhang T, Jia Y, Zhang Y, Yuan H, Zhang G, He C. Indomethacin down-regulating HMGB1 and TNF-α to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. Scand J Gastroenterol. 2019 Jun;**54(6):**793-799. PMID: 31177924 DOI: 10.1080/00365521.2019.1623306

28. **Hosseini Mousalreza,** Shalchiantabrizi P, Yektaroudy K, Dadgarmoghaddam M, Salari M. Prophylactic effect of rectal indomethacin administration, with and without intravenous hydration, on development of endoscopic retrograde cholangiopancreatography pancreatitis episodes: a randomized clinical trial. Arch Iran Med. 2016;19:538–543. 2016 Aug;**19(8):**538-43. PMID: 27544361

29. **Patai Á,** Solymosi N, Patai Á V. Effect of rectal indomethacin for preventing post-ERCP pancreatitis depends on difficulties of cannulation: results from a randomized study with sequential biliary intubation. J Clin Gastroenterol. May-Jun 2015;**49(5)**:429-37. PMID: 25790233 DOI: 10.1097/MCG.0000000000000168.

30. **Sotoudehmanesh R**, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis afterERCP. Am J Gastroenterol. 2007 May;**102(5):**978-83. Epub 2007 Mar 13. PMID: 17355281 DOI: 10.1111/j.1572-0241.2007.01165.x

31. **Kato K,** Shiba M, Kakiya Y, Maruyama H, Ominami M, Fukunaga S, Sugimori S, Nagami Y, Watanabe T, Tominaga K, Fujiwara Y. Celecoxib Oral Administration for Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Randomized Prospective Trial. Pancreas. 2017 Aug;**46(7):**880-886. PMID: 28697127 DOI: 10.1097/MPA.0000000000000852

32. **Mansour-Ghanaei F,** Joukar F, Taherzadeh Z, Sokhanvar H, Hasandokht T. Suppository naproxen reduces incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis: Randomized controlled trial. World J Gastroenterol. 2016;**22:**5114–5121. Published online 2016 Jun 7. DOI: 10.3748/wjg.v22.i21.5114. PMCID: PMC4886387 PMID: 27275104

33. **de Quadros Onófrio F**, Lima J CP, Watte G, Lehmen RL, Oba D, Camargo D, dos Santos CEO. Prophylaxis of pancreatitis with intravenous ketoprofen in a consecutive population of ERCP patients: a randomized double-blind placebo-controlled trial. Surg Endosc. 2017 May;**31(5):**2317-2324. PMID: 27651353 DOI: 10.1007/s00464-016-5234-x

34. **Yokoe M**, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, Itoi T, Sata N, Gabata T, Igarashi H, Kataoka K, Hirota M, Kadoya M, Kitamura N, Kimura Y, Kiriyama S, Shirai K, Takayuki H, Takeda K, Takeyama Y, Hirota M, Sekimoto M, Shikata S, Arata S, Hirata K. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci. 2015;**22:**405–432. PMID: 25973947 DOI: 10.1002/jhbp.259. Epub 2015 May 13.

35. **Chandrasekhara V,** Khashab MA, Muthusamy VR, Acosta RD, Agrawal D, Bruining DH, Eloubeidi MA, Fanelli RD, Faulx AL, Gurudu SR, Kothari S, Lightdale JR, Qumseya BJ, Shaukat A, Wang A, Wani SB, Yang J, DeWitt JM. ASGE Standards of Practice Committee. Adverse events associated with

ERCP. Gastrointest Endosc. 2017;**85**:32–47. Epub 2016 Aug 18. PMID: 27546389 DOI: 10.1016/j.gie.2016.06.051

36. **Sakai P,** Ishioka S, Maluf F et al. Tratado de endoscopia digestiva digestiva diagnóstica e terapêutica. Vias biliares e páncreas. Segunda edição revisada e atualizada – São Paulo/Brasil: Editora Atheneu, 2015.

37. **Serrano JPR,** de Moura DTH, Bernardo WM, Ribeiro IB, Franzini TP, de Moura ETH, Brunaldi VO, Salesse MT, Sakai P, de Moura EGH. Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Endosc Int Open. 2019 Apr; **7(4):** E477–E486. Published online 2019 Apr 2. DOI: 10.1055/a-0862-0215. PMCID: PMC6445649