PJHRD
Philippine Journal of Health Research and Development
University of the Philippines Manila - The Health Sciences Center
Information, Publication and public affairs Office (IPPAO)
8/F Philippine General Hospital Complex, Taft Avenue, Manila 1000 Philippines

Online ISSN: 2783-042X
July-September
VOL. 28 NO. 3 2024
PAGE 20-27

META ANALYSIS

Effectiveness of Rectal Diclofenac in preventing Post-ERCP Pancreatitis (PEP): A meta-analysis

Nicole Allyson A. Chua*, Sergie Paul Christoffer C. Fernandez, and Ismael A. Lapus, Jr.

Department of Internal Medicine, Cardinal Santos Medical Center, San Juan, Philippines
Section of Gastroenterology, Cardinal Santos Medical Center, San Juan, Philippines

ABSTRACT

Background: Post-ERCP pancreatitis (PEP) remains the most common complication following endoscopic retrograde cholangiopancreatography (ERCP). Rectal indomethacin is one of the recommended medications given to prevent pancreatitis in high-risk patients undergoing ERCP.

Objectives: This study aims to evaluate the effectiveness of diclofenac in preventing PEP, to compare its different routes of administration, and to determine the severity of pancreatitis in patients who develop PEP.

Methodology: Databases from PubMed, ScienceDirect and COCHRANE Library were searched for randomized controlled trials (RCTs) comparing diclofenac with placebo in the prevention of PEP up to August 2020. Risk ratio at 95% Confidence Intervals (CI) were calculated to evaluate the incidence of the interested outcomes.

Results: Eleven RCTs with a total population of 2,012 were reviewed in this study. Diclofenac was associated with a significant reduction in overall risk of PEP compared with patients with placebo (RR = 0.59; 95%, 0.47–0.74; P < 0.000001), with a mild heterogeneity (P = 0.05; I2 = 41%). Subgroup analyses showed that rectal diclofenac was the superior choice to significantly reduce the overall incidence of PEP (RR = 0.34; 95%, 0.23-0.51; P < 0.000001).

Conclusion: Rectal diclofenac significantly reduces the risk of PEP and therefore, should be recommended as routine for clinical use in adult patients who will undergo ERCP.

Introduction

1.1 Rationale

Endoscopic Retrograde Cholangiopancreatography (ERCP) is an advanced procedure in the diagnosis and management of pancreatic and biliary system disorders [1]. Although it has many advantages compared with other traditional modalities, it also comes with various complications. Among the complications that were reported in many literatures, post-ERCP pancreatitis (PEP) remains the most common one, which occurs in approximately 3% to 15% of ERCP cases, 5% of which having a severe course of the condition resulting in prolonged hospitalization and in need of further procedure and management [1-3].

In literature, pathogenesis of PEP is not well understood, but authors have postulated that pancreatic duct imaging and/or instrumentation initiate inflammatory cascade leading to pancreatitis [3]. Starting with intracellular changes followed by pancreatic acinar cell damage leading to local inflammatory response which causes release of chemokines and subsequently proinflammatory cytokine into the circulation leading to activation of the inflammatory cascade. Phospholipase A2 may play a vital role in the initial inflammatory cascade of acute pancreatitis and identifying pharmacologic agents that inhibit or disturb this cascade may prevent or limit the pancreatitis and its consequences. Diclofenac and indomethacin both inhibit phospholipase A2. Inhibition of phospholipid A2 results in suppression of several proinflammatory molecules (prostaglandins, leukotrienes, and platelet-activating factor). NSAIDs further inhibit neutrophil-endothelial cell binding [29].

Several studies have shown the impact of different pharmacologic therapy in the prevention of PEP, of which, the use of non-steroidal anti-inflammatory drugs (NSAIDs) gave the most promising results due to the fact that it can inhibit prostaglandin synthesis, terminating the inflammatory cascade of pancreatitis [2,3].

Presently, a number of trials and meta-analyses showed the efficacy and safety of NSAIDs in the prevention of PEP [2-5] however few studies [21,22] were done to determine which route of administration is the most effective in the prevention of the said complication. Despite these studies, the use of rectal NSAIDs have not been widely used in clinical practice.

Diclofenac, an NSAID, is cheap, easily administered, with various drug routes of administration readily available, and has a favorable risk profile when given a standard dose (50 mg or 100 mg), making it an attractive option in the prevention of post-ERCP pancreatitis. In some randomized controlled trials (RCTs), different oral and suppository forms of diclofenac have shown promising prophylactic activity with regard to PEP, however, some studies still yield conflicting results.

To provide an update and a framework for future research in this important area, we therefore conducted a meta-analysis of randomized controlled trials currently available and evaluate the effectiveness of diclofenac in the prevention of post-ERCP pancreatitis.

1.2 Objectives

The general objective of this study is to evaluate the effectiveness of diclofenac in preventing post-ERCP pancreatitis. The specific objectives are as follows: to compare the different routes of administration of diclofenac in terms of incidence of PEP, and to determine the severity of pancreatitis in patients who develop PEP.

1.3 Statement of the Problem

This study seeks to answer the question: Among patients who will undergo ERCP, is diclofenac effective in preventing post-ERCP pancreatitis?

Corresponding author's email address:
nicoleallysonchua@gmail.com
Keywords: NSAIDs, diclofenac, Endoscopic Retrograde Pancreatography (ERCP), Pancreatitis, Post-ERCP Pancreatitis (PEP)

Methodology

2.1 Protocol and Registration

A review protocol is available upon request from the primary investigators. This study, with registration information CRC TM 2020-61, was technically reviewed and approved by the Cardinal Santos Medical Center Research Team on October 15, 2020. Protocols and all required forms were also submitted to and reviewed by the Research Ethics Review Committee (RERC).

2.2 Eligibility Criteria

Articles were included if they met the following criteria: (1) the study was a prospective, randomized controlled trial (RCT); (2) compared diclofenac with placebo; (3) examined the role of diclofenac in the prevention of post-ERCP pancreatitis using different routes of administration regardless of timing; (4) original data not duplicated in another manuscript.

Cohort studies, case-control studies, case reports and case series were excluded. If more than one version of the same study was retrieved, only the most complete or the latest one was used. Ethical approval and patient consent were not applicable for meta-analysis.

2.3 Search Strategy

A comprehensive and systematic search was used to retrieve relevant randomized controlled trials studies using the following databases: PubMed, Science Direct and COCHRANE Library for studies of diclofenac in the prevention of post-ERCP pancreatitis updated to August 2020.

Keywords and/or medical subject heading terms used were as follows: (diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis).

An expanded search was done using Boolean operators and MESH. The search was restricted to trials on adult humans. No date and language restrictions were applied.

Duplicates were removed, screened as to the relevance to the intended outcome. The obtained set of journals were assessed for eligibility by utilizing the inclusion and exclusion criteria. The remaining set of journals were the studies included in the meta-analysis appraisal.

Disagreements were resolved by joint discussion to reach consensus. When necessary, authors would be contacted for further information.

2.4 Study Selection

Studies were selected after careful title and abstract screening. Data extraction was independently performed by two (2) reviewers according to the prespecified eligibility criteria. Duplicates were removed manually.

Full text articles were assessed independently by the two reviewers according to its eligibility, with reporting exclusion reasons of articles. Disagreements were resolved by joint discussion between the two authors and a third reviewer.

2.5 Data Collection Process

Records were identified through database searching using the mentioned search terms. Duplicates were removed. Title and abstracts were screened and full-text articles were assessed for eligibility.

Qualified studies were identified and included in the final analysis. The following information from each study was extracted: first author, publication year, study location, study design, patient characteristics, sample size, intervention approaches (drug form, route, dose and timing), and severity criteria.

In addition, the outcome data of studies, including the number and the severity of post-ERCP pancreatitis (any, mild, moderate, severe).

2.6 Risk of Bias Assessment in Individual Studies

The quality of the included RCTs were assessed according to the methodological criteria of the Cochrane Handbook for Systematic Reviews of Interventions.

We assessed the risk of bias through seven domains, including allocation sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, management of incomplete outcome data, selective outcome reporting, and other potential sources of bias using RevMan 5.4 software.

The two reviewers independently appraised each journal according to these biases and compared the results. Disagreements were resolved by joint discussion between the two authors and a third reviewer. Funnel plots were assessed visually to check for publication bias due to different sample sizes.

2.7 Statistical Analysis

The meta-analysis was performed in accordance with the recommendations of Cochrane Collaboration using RevMan 5.4 software.

For dichotomous data, results were expressed as risk ratios (RRs) with the corresponding 95% confidence intervals (CIs). For continuous data, weighted mean difference (WMD) with 95% CIs was calculated.

Visual inspection of the forest plots were used to identify the statistical heterogeneity, which was further complemented by the I2 inconsistency test, to quantify inconsistency across studies resulting from heterogeneity rather than from chance.

If no heterogeneity between studies ($P > 0.1$, $I2 < 50\%$) were noted, a meta-analysis of intention-to-treat data was performed using the fixed-effect model Mantel-Haenszel method instead.

For statistically significant treatment effects, the number needed to treat (NNT) to prevent 1 episode of PEP was calculated using the absolute risk reduction (ARR): NNT = 1/ARR. Statistical significance was judged if $P < 0.05$, except where otherwise specified.

Results

3.1 Study Selection

The initial search yielded 249 relevant records of which a total of 186 were excluded because of duplicate data or based on the screening of titles and abstracts (Figure 1). The remaining 63 studies were retrieved for full-text review. Fifty-two of these studies were excluded for the following reasons: 29 studies made use of interventions other than diclofenac, 4 studies were not of the adult population and 19 of the studies were not randomized controlled trials. Finally, 11 studies that included a total of 2012 patients, published from 2003 through 2020, were identified and analyzed in this review.

3.2 Study Characteristics

Of the 11 studies, 2 studies were conducted in Japan [17,20], 1 in South Korea [18], 2 in Malaysia [13,19], 1 study in Italy [10], 1 in Scotland [14], 1 in Turkey [11], 1 in Iran [16], 1 in Pakistan [12], and 1 in USA [15]. Sample sizes ranged from 20 to 205, and incidence rates of PEP in the control group varied from 9.4% to 40.7%.

Diclofenac was administered rectally in 5 studies [12,14,16,17,19], orally in 2 studies [18,20], intramuscularly in 1 study [18], intravenously in 1 study [13], orally/rectally/intramuscularly/intravenously in 1 study [10], and intramuscular/rectally in 1 study [11]. The study drug was administered pre-ERCP only in 5 studies [11,12,17,19,20], post-ERCP only in 4 studies [14-16,18], or both pre- and post-ERCP in 2 studies [10,13]. Diclofenac 50 mg was used in 2 studies [15,20], 75 mg in 1 study [13], 90 mg in 1 study [18], 100 mg in 4 studies [12,14,16,19]. Multiple doses of diclofenac were used in 3 studies (50mg/75mg/100mg[10]; 75mg/100mg[11]; 25mg/50mg[17]) depending on the route used. Two studies used the definition of post-ERCP pancreatitis based on the consensus criteria [10,11], on the other hand, 5 studies defined post-ERCP pancreatitis as an increase in serum amylase 3x greater than the upper limit of normal and new onset or worsened abdominal pain lasting more than 24 hours after procedure [13,15,17,18,20]. Three studies described PEP as epigastric pain with elevated amylase levels greater than four-fold the upper limit of normal [14,16,19], and 1 study did not mention how they defined PEP [12]. To assess the severity of PEP, out of the 11 studies, 5 studies used duration of hospital stay [11,12,15,17,19], 2 studies used treatment duration [18,20], and the remaining studies did not mention level of PEP severity [10,13,14,16].

In general, the baseline characteristics of patients and procedures were consistent across two groups in each study. Basic characteristics of included studies and the main outcome data of each included study are summarized in the tables found in Appendix A.

3.3 Quality Assessment

The summary of the risk bias assessment of the studies used is shown in Figures 2 and 3. Blinding evaluation was satisfactory in 10 of the 11 studies used. High risk bias was assigned to the study by Lua, *et al.* [15] as it was an open-labelled study. Three [10,13,18] of the 11 studies were labelled as high risk for attrition bias because not all the randomized participants were included in the final analysis. The study by Park, *et al.* [18] likewise was deemed as high risk for reporting bias because the outcomes of the excluded participants in their study were not reported.

Publication bias was analyzed using funnel plots (Appendix C). The study showed no significant publication bias by visual inspection of asymmetry in the incidence of PEP, regardless of severity.

3.4 Synthesis of Results

Analyses of the effectiveness of diclofenac in preventing PEP (Figure 4) showed no to mild heterogeneities among the subgroups with I2 values ranging from 0% (risk of PEP in intravenous, oral and rectal routes), to 45% (risk of PEP in the intramuscular route), with mild heterogeneity overall (I2 = 41%).

Overall Incidence of Post-ercp Pancreatitis

Post-ERCP pancreatitis was documented in 98 of 1056 patients (9.3%) administered with diclofenac, compared with 167 of 1059 (15.8%) with placebo or no treatment. Pooling of data showed that diclofenac was associated with a significant reduction in overall risk of PEP compared with patients with placebo or no treatment (RR = 0.59; 95%, 0.47–0.74; P < 0.000001), with a mild heterogeneity (P = 0.05; I2 = 41%). Subgroup analysis showed that among the four routes of administration, rectal diclofenac was associated with a statistically significant reduction in the overall risk of PEP (RR = 0.34; 95%, 0.23-0.51; P < 0.000001), whereas the intramuscular route (RR = 0.83; 95%, 0.51-1.35; P = 0.45), intravascular route (RR = 0.35; 95% 0.12-1.04; P = 0.06) and oral route (RR = 0.98; 95% 0.65-1.48; P = 0.93), were all statistically insignificant. Figure 4 shows the forest plot comparing diclofenac and placebo on the incidence of PEP, along with their corresponding subgroup analysis.

Severity of Pancreatitis

Seven studies [10,12,13,15,17,18,20] provided data on the severity of post-ERCP pancreatitis. There was no statistical difference in the severity of pancreatitis among the different routes of administration of diclofenac (Figures 5, 6, 7), with a risk ratio of 0.84 (p = 0.33), 0.64 (p = 0.10) and 0.80 (p = 0.73) for mild, moderate and severe pancreatitis, respectively.

Analyses of the effectiveness of diclofenac in preventing mild pancreatitis (Figure 5) showed no evidence of heterogeneity among the subgroups except for the intravenous route (not applicable) due to the lack of comparative studies.

Mild pancreatitis was documented in 54 of 783 patients (6.9%) administered with diclofenac, compared with 64 of 782 patients (8.2%) with placebo or no treatment. Pooling of data shows that diclofenac, regardless of route of administration (IM, IV, oral or rectal), has a lesser incidence of mild pancreatitis but it was not statistically significant (RR = 0.84; 95%, 0.60-1.19; P = 0.33). Figure 5 shows the forest plot comparing diclofenac and placebo on the incidence of mild pancreatitis, along with their corresponding subgroup analysis.

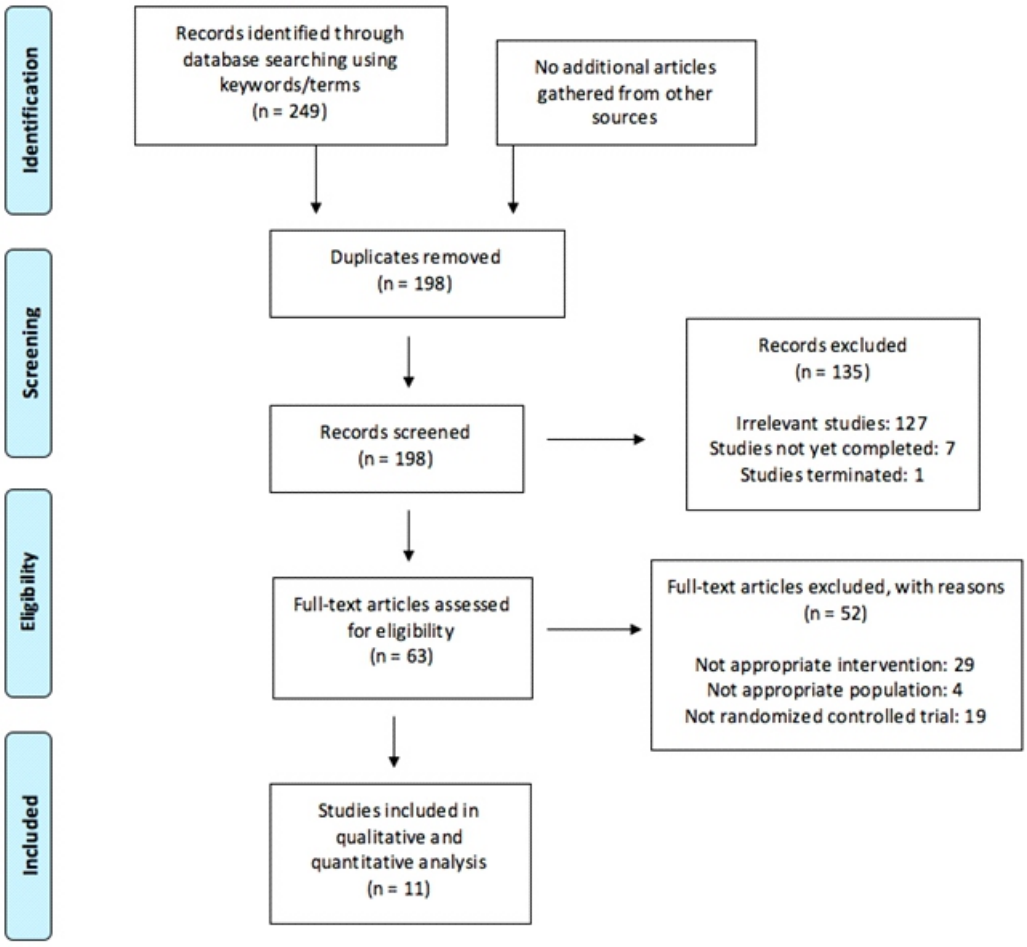


Figure 1. Study Search Diagram based on the PRISMA Guideline

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

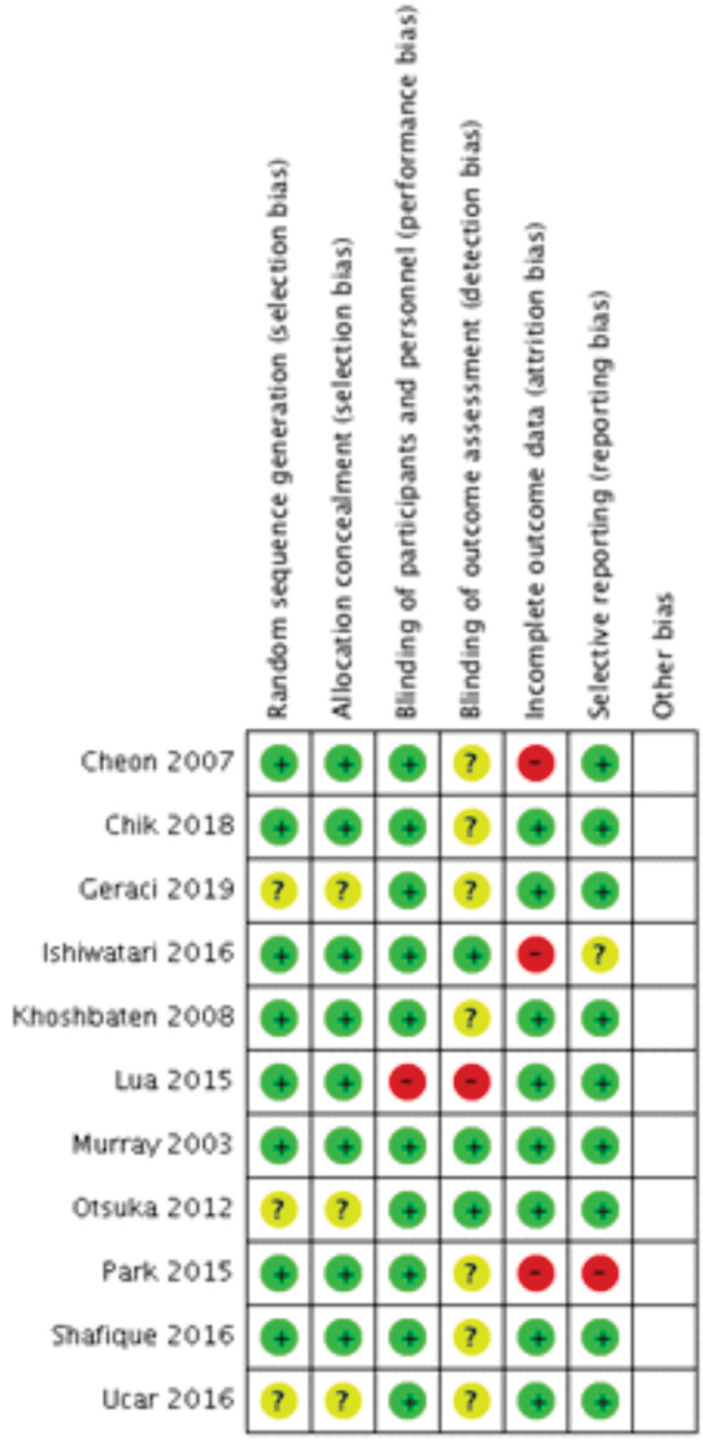


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Analyses of the effectiveness of diclofenac in preventing moderate pancreatitis (Figure 6) showed no evidence of heterogeneity among the intramuscular and oral routes, and mild heterogeneity in the rectal route (43%). Heterogeneity was not applicable for the intravenous route.

Moderate pancreatitis was documented in 19 of 783 patients (2.4%) administered with diclofenac, compared with 31 of 782 patients (4.0%) with placebo or no treatment. Pooling of data shows that diclofenac, regardless of route of administration (IM, IV, oral or rectal), has a lesser incidence of moderate pancreatitis but it was not statistically significant (RR = 0.64; 95%, 0.38-1.09; P = 0.10). Figure 6 shows the forest plot comparing diclofenac and placebo on the incidence of moderate pancreatitis, along with their corresponding subgroup analysis.

Analyses of the effectiveness of diclofenac in preventing severe pancreatitis (Figure 7) showed no evidence of heterogeneity in the oral route, and was not applicable to the rest of the subgroups.

Severe pancreatitis was documented in 4 of 783 patients (0.5%) administered with diclofenac, compared with 5 of 782 patients (0.64%) with placebo or no treatment. Pooling of data shows that diclofenac has a lesser incidence of severe pancreatitis but it was not statistically significant (RR = 0.80; 95%, 0.23-2.78; P = 0.28). The subgroup analysis of intramuscular diclofenac showed that it favored placebo in preventing severe pancreatitis, but it was not statistically significant (RR = 4.91; 95%, 0.24-101.60; P =0.30). All the other routes (IV and rectal) were not estimable. Figure 7 shows the forest plot comparing diclofenac and placebo on the incidence of severe pancreatitis, along with their corresponding subgroup analysis.

Discussion

4.1 Summary of Evidence

In this meta-analysis of 11 RCTs that included 2012 patients, there was evidence to suggest that diclofenac was associated with about a 41% decrease in the risk of developing post-ERCP pancreatitis. The ARR was 6.5% (95% CI, 3.6-9.3%) and the NNT was 15. Furthermore, the evidence suggests that among the different routes of administration, rectal diclofenac showed a significant reduction in the incidence of PEP at 66%. The ARR was 13.5% (95% CI, 8.9-18%) and the NNT was 7.

After stratifying studies according to the severity of post-ERCP pancreatitis, evidence shows a decreased risk was recognized in mild, moderate and severe post-ERCP pancreatitis (16%, 33% and 20%, respectively), with the use of diclofenac when compared to placebo, although it was statistically insignificant.

The present findings are consistent with the ACG 2013, ESGE 2014 and JSHBPS 2015 guidelines in which rectal diclofenac is widely recommended in preventing post-ERCP pancreatitis in all patients with no contraindications [23-25]. However, the study by Lua *et al.* [15] suggested that there is no significant association between rectal diclofenac and the decrease in incidence of post-ERCP pancreatitis among subjects. These findings conflict with these proposed guidelines. There were 6 previous meta-analyses [5,21,22,26-28] on the effectiveness of NSAIDs in preventing PEP; three of which included indomethacin or diclofenac vs placebo [5,26,28], and the remaining 3 studies included other NSAIDs such as naproxen [21,22,28], valdecoxib [21], ketoprofen [21] and flurbiprofen [22].

Our meta-analysis is, to our knowledge, the first to focus on the effectiveness of diclofenac, specifically. The present findings are consistent with these 6 previous meta-analyses [5,21,22,26-28], such that diclofenac, an NSAID, is effective in the overall prevention of PEP. Only 1 meta-analysis [26] showed that intramuscular diclofenac was effective in decreasing the risk of pancreatitis. This inconsistency might be because rectal administration is the most commonly used method in clinical practice; whereas other routes are not widely studied yet.

Our study was not able to show a significant reduction on the different types of severity of pancreatitis (mild, moderate and severe) with the use of diclofenac. In contrast to this, 2 previous studies [5,21] reported a significant reduction in mild pancreatitis, and 2 other previous studies [5,28] reported a significant reduction in moderate to severe pancreatitis with the use of

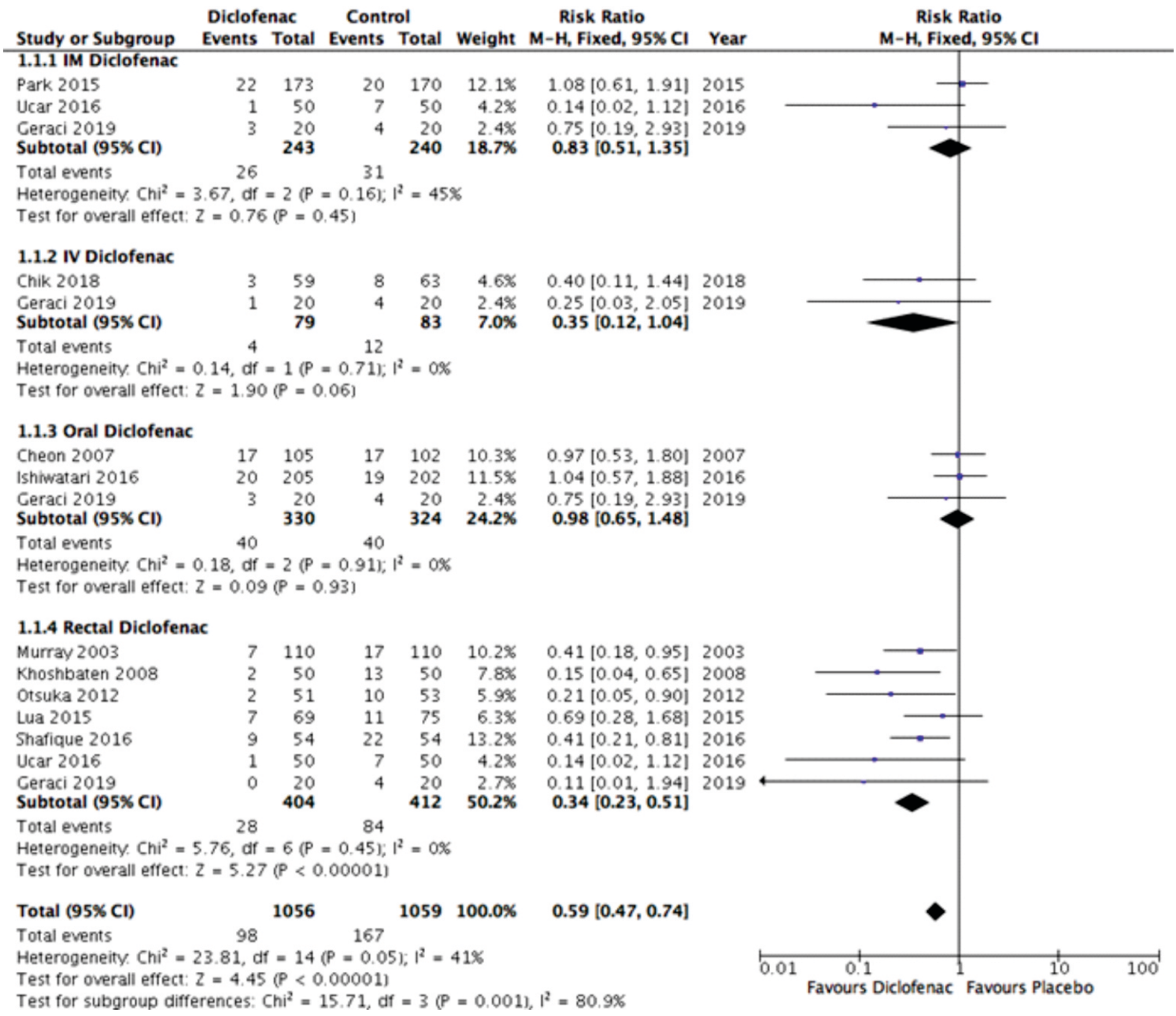


Figure 4. Forest plot of comparison on diclofenac and the incidence of post-ERCP pancreatitis.

NSAIDs. This inconsistency might be due to the higher number of large-scale RCTs available on indomethacin when compared to diclofenac. This might also be the reason why in the study of Liu *et al*. [22], indomethacin was more superior in preventing severe pancreatitis when compared to diclofenac.

Due to the small number of RCTs published in the literature, it was not possible to identify whether another route of administration (oral, intravenous and intramuscular), timing of administration, and dosing are effective in preventing PEP.

Study Limitations

Limitations of this meta-analysis must be considered. First, we found mild heterogeneity across the studies in our meta-analysis. Given the difference in the data source, study population, the timing and route of administration, and study design, this may be expected. Second, the patient characteristics, diagnostic criteria of pancreatitis and its severity, as well as the intervention regimen varied across studies, which may influence the results, thereby limiting comparability to some extent. Significant differences between two groups might result from type 1 error, and need to be further investigated. Third, there may have been potential publication bias in this meta-analysis since we were not able to include some unpublished papers because the data was not available to us.

Conclusions and Recommendations

This meta-analysis provides evidence that rectal diclofenac significantly reduces the risk of post-ERCP pancreatitis and therefore should be recommended as routine for clinical use in adult patients who will undergo ERCP. Ideally, more large-scale multicenter RCTs should be conducted in the future to compare different routes of diclofenac, different doses and timing of administration (pre-procedure versus post-procedure), to determine the best NSAID (diclofenac vs other NSAIDs), optimal dose and timing of administration in the prevention of acute pancreatitis after ERCP. Decisions on NSAIDs may be influenced by local availability and costs, hence a cost-effectiveness study of the types of NSAIDs to decrease the incidence of PEP should be conducted as well.

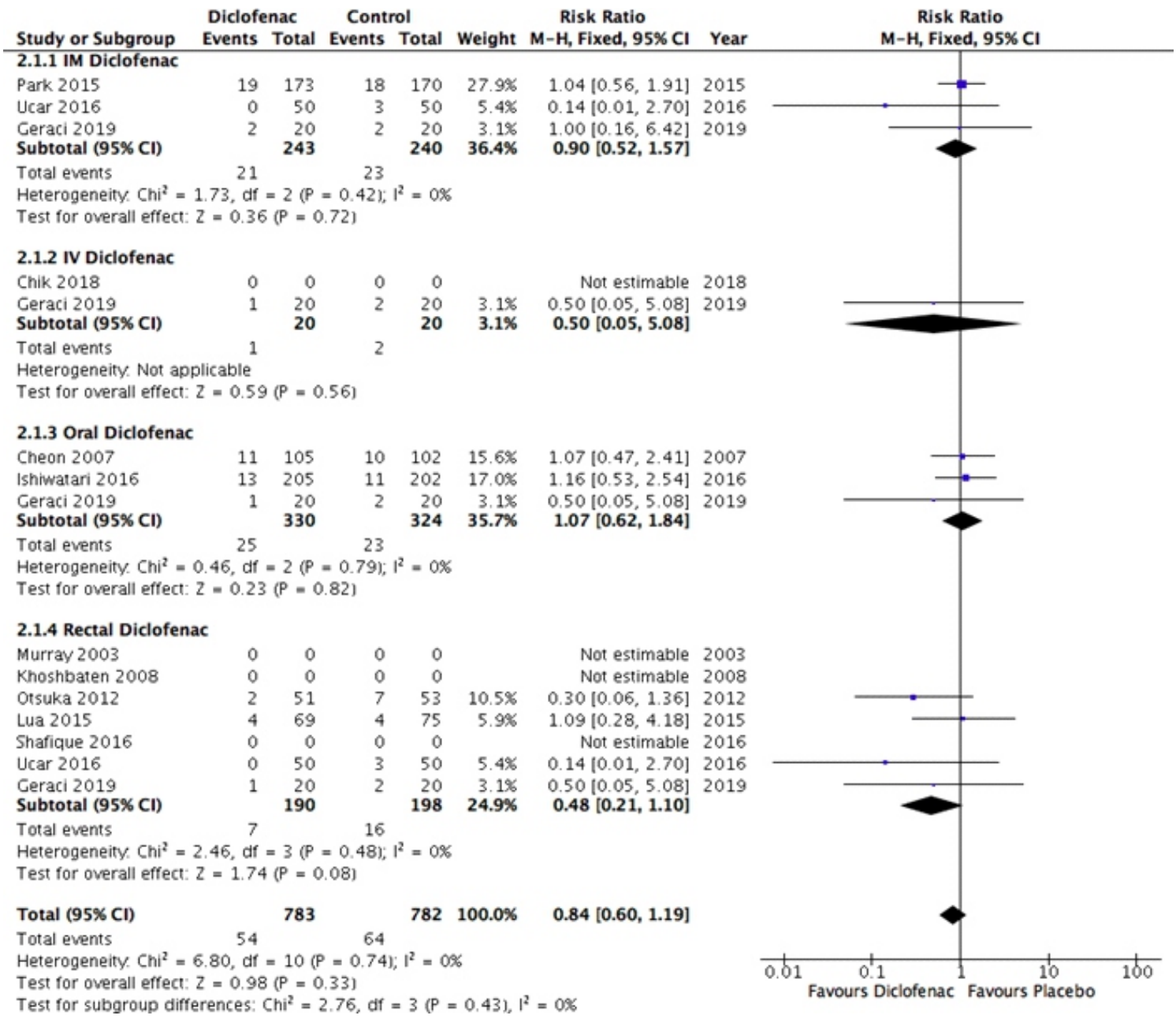


Figure 5. Forest plot of comparison on diclofenac and mild pancreatitis.

References

1. Zheng MH, Meng M Bin, Gu DN, Zhang L, Wu AM, Jiang Q, *et al.* (2009) Effectiveness and tolerability of NSAIDs in the prophylaxis of pancreatitis after endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis. Current Therapeutic Research - Clinical and Experimental. 70:323-334
2. Mazaki T, Mado K, Masuda H, Shiono M. (2014) Prophylactic pancreatic stent placement and post-ERCP pancreatitis: An updated meta-analysis. J Gastroenterol. 49(2) 343-355
3. Sun HL, Han B, Zhai HP, Cheng XH, Ma K. (2014) Rectal NSAIDs for the prevention of post-ERCP pancreatitis: A meta-analysis of randomized controlled trials. Surgeon.
4. Ding X, Chen M, Huang S, Zhang S, Zou X. (2012) Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: A meta-analysis. Gastrointest Endosc. 76(6), 1252–1259.
5. Hou YC, Hu Q, Huang J, Fang JY, Xiong H. (2017) Efficacy and safety of rectal nonsteroidal anti-inflammatory drugs for prophylaxis against post- ERCP pancreatitis: A systematic review and meta-analysis. Sci Rep. 7(March):1–13.
6. Gan TJ. (2010) Diclofenac: an update on its mechanism of action and safety profile. Curr Med Res Opin. 26(7):1715-31
7. Baiu I, Visser B. (2018) Endoscopic Retrograde Cholangiopancreatography. JAMA. 320(19)
8. Basnayake C, Ratnam D. (2015) Blood tests for acute pancreatitis. Aust Prescr. 38(4):128-30
9. Da Silva AM & Willmore LJ. (2012) Posttraumatic epilepsy. Epilepsy, 585–599.
10. Cheon YK, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, *et al.* (2007) Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc. 66(6):1126–32.
11. Chik IAN, Jarmin R, Ariffin A, Othman H, Zuhdi Z, Azman A, *et al.* (2018) A less invasive method of reducing the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis: Intravenous diclofenac sodium versus placebo. Asian J Pharm Clin Res. 11(10):140–4.
12. Geraci G, Palumbo VD, D'Orazio B, Maffongelli A, Fazzotta S, Lo

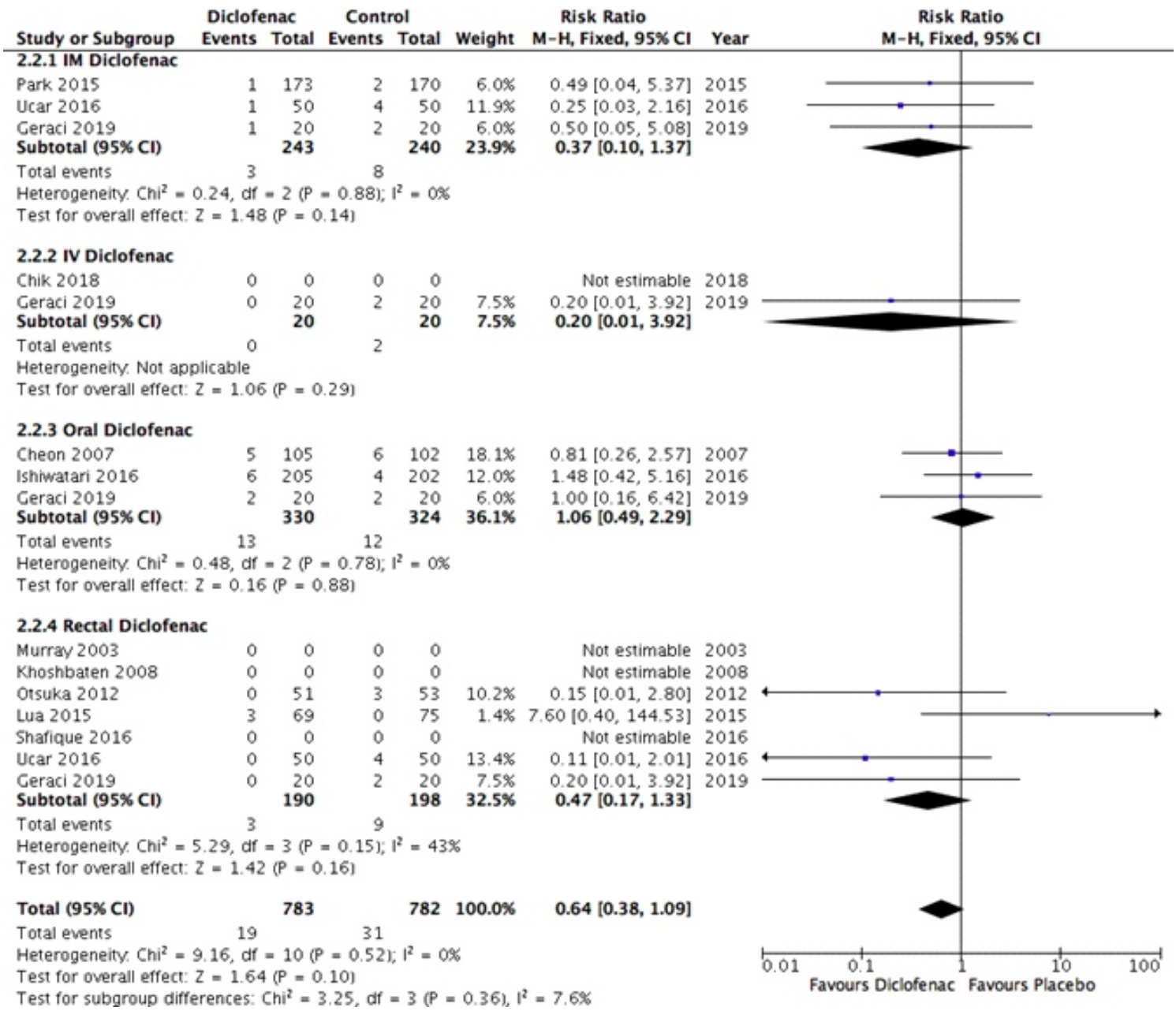


Figure 6. Forest plot of comparison on diclofenac and moderate pancreatitis.

Monte AI. (2019) Rectal diclofenac administration for prevention of post-endoscopic retrograde cholangio-pancreatography (ERCP) acute pancreatitis. Randomized prospective study. Clin Ter. 170(5):E332–6.

13. Ishiwatari H, Urata T, Yasuda I, Matsusaki S, Hisai H, Kawakami H, *et al.* (2016) No Benefit of Oral Diclofenac on Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis. Dig Dis Sci. 61(11):3292–301.
14. Khoshbaten M, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. (2008) Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 23(7 PT2).
15. Lua GW, Muthukaruppan R, Menon J. (2015) Can Rectal Diclofenac Prevent Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis? Dig Dis Sci. 60(10):3118–23.
16. Murray B, Carter R, Imrie C, Evans S, O'suilleabhain C. (2003) Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology. 124(7):1786–91.
17. Otsuka T, Kawazoe S, Nakashita S, Kamachi S, Oeda S, Sumida C, *et al.* (2012) Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: A randomized controlled trial. J Gastroenterol. 47(8):912–7.
18. Park SW, Chung MJ, Oh TG, Park JY, Bang S, Park SW, *et al.* (1998) Intramuscular diclofenac for the prevention of post-ERCP pancreatitis: A randomized trial. Endoscopy. 47(1):33–9.
19. Shafique MS, Khan JS, Fayyaz MU, Zafar S, Nasrullah M, Ahmad R. (2016) Prophylactic rectal NSAIDS in the prevention of POST-ERCP pancreatitis. J Postgrad Med Inst. 30(2):184–8.
20. Uçar R, Biyik M, Uçar E, Polat İ, Çifçi S, Ataseven H, *et al.* (2016) Rectal or intramuscular diclofenac reduces the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography. Turkish J Med Sci. 46(4):1059–63.
21. Serrano J, de Moura D, Bernardo W, Ribeiro I, Franzini T, de Moura E, *et al.* (2019) Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Endosc Int Open. 07(04) E477-E486
22. Liu L, Li C, Huang Y, Jin H. (2019) Nonsteroidal Anti-inflammatory Drugs for Endoscopic Retrograde Cholangiopancreatography Postoperative Pancreatitis Prevention: a Systematic Review and Meta-analysis. J Gastrointest Surg. 23(10), 1991–2001.
23. Isaji S, Takada T, Mayumi T, Yoshida M, Wada K, *et al.* (2015)

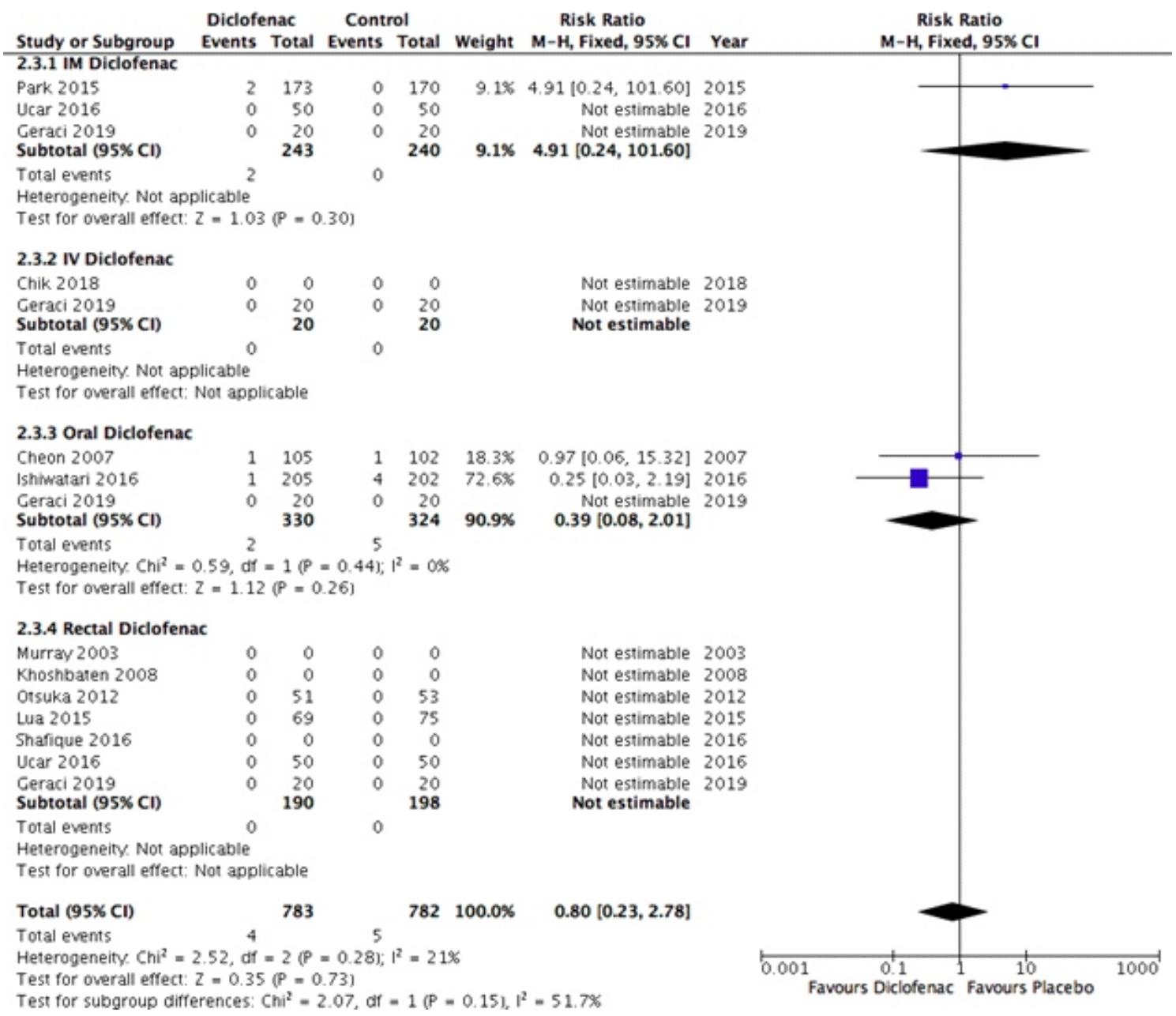


Figure 7. Forest plot of comparison on diclofenac and severe pancreatitis.

Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points. J Hepatobiliary Pancreat Sci. 22(6):433-45.

24. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, *et al.* (2014) European Society of Gastrointestinal Endoscopy. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy. 46(9):799-815.
25. Tenner S, Baillie J, DeWitt J, Vege SS, (2013) American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 108(9):1400-15; 1416. doi: 10.1038/ajg.2013.218. Epub 2013 Jul 30. Erratum in: Am J Gastroenterol. 2014 Feb;109(2):302.
26. Li L, Han Z, Yuan H, Zhang G, Jia Y, He C. (2017) Nonsteroidal anti-inflammatory drugs reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis. J Hepatobiliary Pancreat Sci. 24(9):520-529.
27. Yang C, Zhao Y, Li W, Zhu S, Yang H, *et al.* (2017) Rectal nonsteroidal anti-inflammatory drugs administration is effective for the prevention of post-ERCP pancreatitis: An updated meta-analysis of randomized controlled trials. Pancreatology. 17(5):681-688.
28. Shen C, Shi Y, Liang T, Su P. (2017) Rectal NSAIDs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in unselected patients: Systematic review and meta-analysis. Dig Endosc. 29(3):281-290.
29. Döbrönte Z, Szepes Z, Izbéki F, Gervain J, Lakatos L, *et al.* (2014) Is rectal indomethacin effective in preventing of post-endoscopic retrograde cholangiopancreatography pancreatitis? World J Gastroenterol. 20:10151–10157.

Appendix A

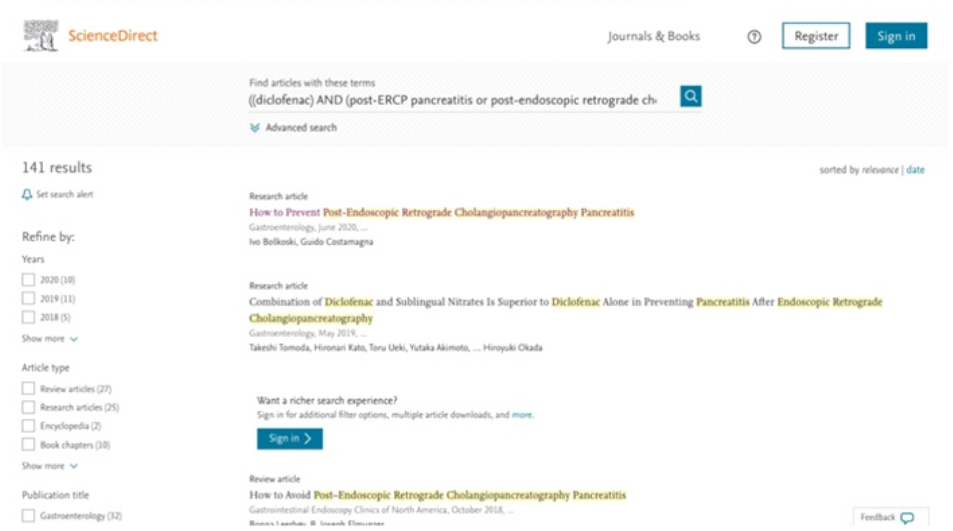
Literature Search Strategies

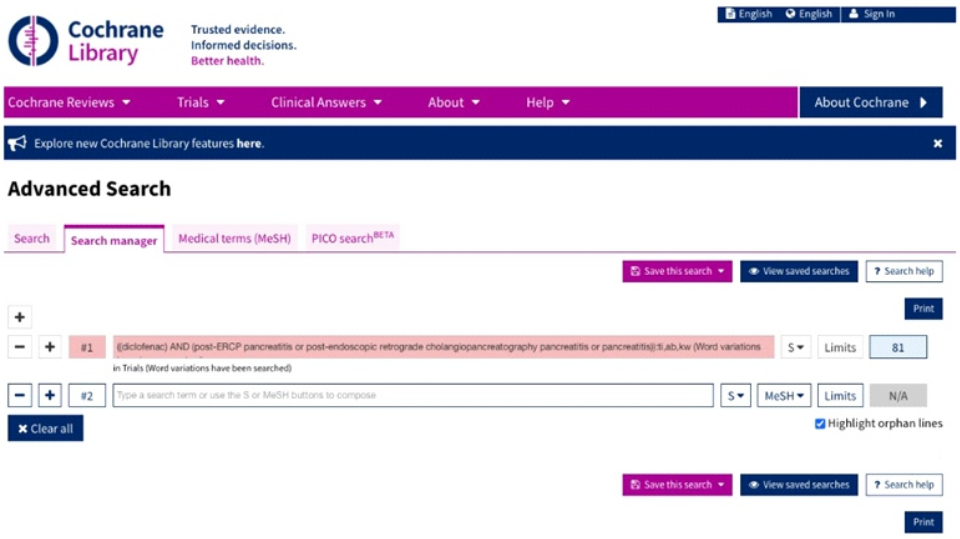
PubMed Advanced Search Builder

History and Search Details

Search	Actions	Details	Query	Results	Time
#6	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))** Filters: **Full text, Randomized Controlled Trial, Humans, English, Adult: 19+ years**	18	06:18:03
#5	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))** Filters: **Full text, Randomized Controlled Trial, Humans, English**	20	06:17:58
#4	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))** Filters: **Full text, Randomized Controlled Trial, Humans**	20	06:17:41
#3	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))** Filters: **Full text, Randomized Controlled Trial**	20	06:17:14
#2	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))** Filters: **Randomized Controlled Trial**	20	06:17:10
#1	•••	›	Search: **(Therapy/Broad[filter]) AND ((diclofenac) AND (post-ERCP pancreatitis or post-endoscopic retrograde cholangiopancreatography pancreatitis or pancreatitis))**	81	06:16:53

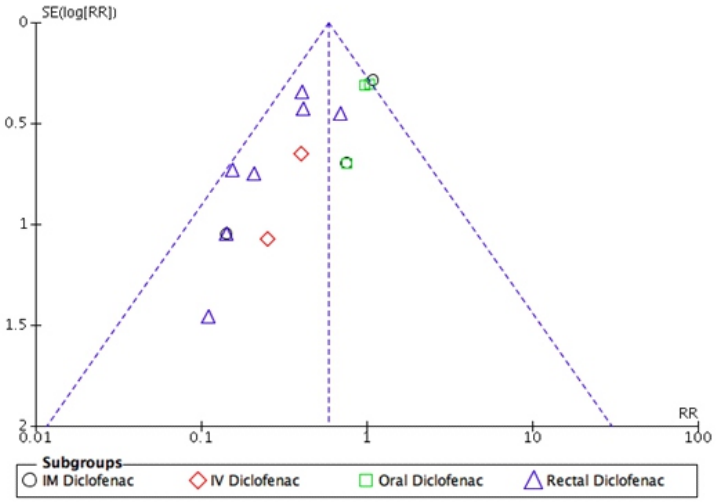
Showing 1 to 6 of 6 entries



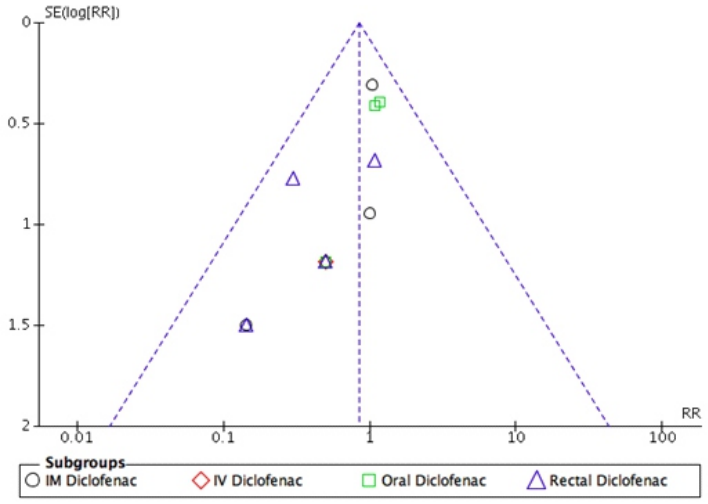


Appendix C

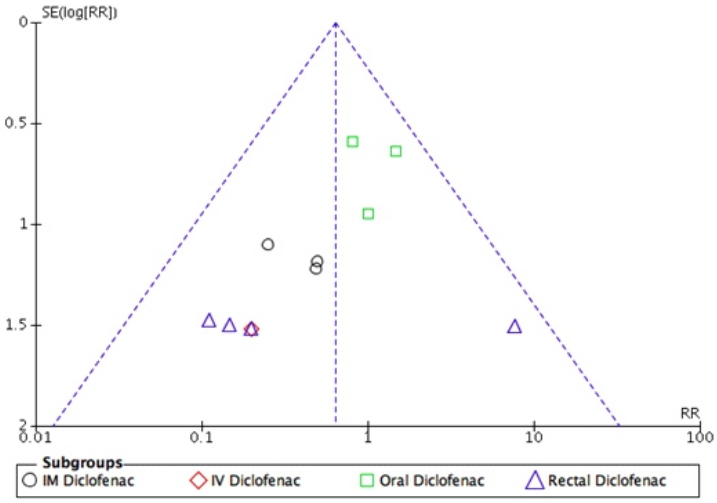
Funnel Plot on the Comparison of Diclofenac and the Incidence of Post-ERCP Pancreatitis



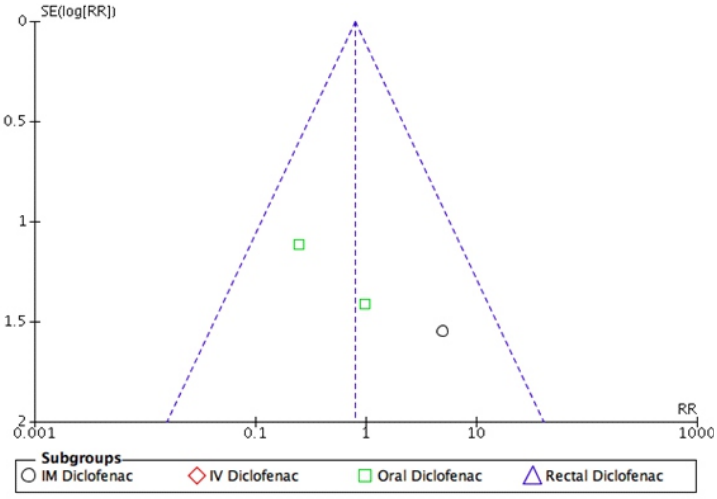
Funnel Plot on the Comparison of Diclofenac and Mild Pancreatitis



Funnel Plot on the Comparison of Diclofenac and Moderate Pancreatitis



Funnel Plot on the Comparison of Diclofenac and Severe Pancreatitis



Appendix B

Design and Baseline Characteristics of Included Trials

Source	Text	Setting	Age (Mean±SD)	Sample size	Intervention				Severity Criteria
					Drug	Route	Dose	Timing	
Geraci, 2019, Italy	Full	Single center	I (IM): 61.2 (60-77) I (Oral): 60.1 (55-71) I (Rectal): 59.8 (54-75) I (IV): 60.3 (51-76) C: 58.6 (55-72)	100	I: Diclofenac C: Placebo	Oral/ Rectal/ IM/ IV	50mg/ 100mg/ 75mg/ 75mg	30-90 mins pre-ERCP	Duration of hospital stay
Ucar, 2016, Turkey	Full	Single center	I (IM): 61.1 ± 16.8 I (Rectal): 59 ± 18.6 C: 60.5 ± 17.6	150	I: Diclofenac C: Placebo	IM/ Rectal	75mg/ 100mg	30-90 mins pre ERCP	Duration of hospital stay
Shafique, 2016, Pakistan	Full	Single center	I: 46.09 ± 12.31 C: 42.93 ± 14.69	108	I: Diclofenac C: Glycerine	Rectal	100mg	Immediately pre-ERCP	N/A
Chik, 2018, Malaysia	Full	Single center	I: 52.86 ± 4.01 C: 55.70 ± 4.22	122	I: Diclofenac C: Placebo	IV	75mg	30 mins pre-ERCP	N/A
Murray, 2003, Scotland	Full	Single center	I: 55 ± 15 C: 58 ± 14	220	I: Diclofenac C: Placebo	Rectal	100mg	Immediately post-ERCP	N/A
Cheon, 2007, USA	Full	Single center	I: 45.6 C: 46.0	207	I: Diclofenac C: Placebo	Oral	50mg	30-90 mins pre and 4-6 hours post ERCP	Duration of hospital stay
Khoshbaten, 2008, Iran	Full	Single center	I: 57 ± 15 C: 60 ± 17	100	I: Diclofenac C: Placebo	Rectal	100mg	Immediately post-ERCP	N/A
Otsuka, 2012, Japan	Full	Single center	N/A	104	I: Diclofenac C: Placebo	Rectal	25mg/50mg	30 mins pre-ERCP	Duration of therapeutic intervention
Park, 2015, South Korea	Full	Single center	I: 63.94 ± 12.93 C: 64.93 ± 13.71	343	I: Diclofenac C: Placebo	IM	90mg	Immediately post-ERCP	Treatment duration
Lua, 2015, Malaysia	Full	Single center	I: 50.3 ± 17.6 C: 49.6 ± 16.8	151	I: Diclofenac C: No intervention	Rectal	100mg	Immediately post-ERCP	Duration of hospital stay
Ishiwatari, 2016, Japan	Full	Multi center	I: 70.4 ± 10.3 C: 68.9 ± 11.8	407	I: Diclofenac C: Placebo	Oral	50mg	Immediately pre and post-ERCP	Treatment duration

Main Outcome Data of Studies Included in the Meta-Analysis

Study	Severity of Pancreatitis			
	Any incidence of PEP	Mild	Moderate	Severe
Geraci, 2019, Italy	I (Oral): 3 I (Rectal): 0 I (IM): 3 I (IV): 1 C: 4	I (Oral): 1 I (Rectal): 0 I (IM): 2 I (IV): 1 C: 4	I (Oral): 2 I (Rectal): 0 I (IM): 1 I (IV): 0 C: 4	I (Oral): 0 I (Rectal): 0 I (IM): 0 I (IV): 0 C: 4
Ucar, 2016, Turkey	I (IM): 1 I (Rectal): 1 C: 7	I (IM): 1 I (Rectal): 0 C: 3	I (IM): 1 I (Rectal): 0 C: 4	I (IM): 0 I (Rectal): 0 C: 0
Shafique, 2016, Pakistan	I: 9 C: 22	N/A	N/A	N/A
Chik, 2018, Malaysia	I: 3 C: 8	N/A	N/A	N/A
Murray, 2003, Scotland	I: 7 C: 17	N/A	N/A	N/A
Cheon, 2007, USA	I: 17 C: 17	I: 11 C: 10	I: 5 C: 6	I: 1 C: 1
Koshbaten, 2008, Iran	I: 2 C: 13	N/A	N/A	N/A
Otsuka, 2012, Japan	I: 2 C: 10	I: 2 C: 7	I: 0 C: 3	None
Park, 2015, South Korea	I: 22 C: 20	I: 19 C: 18	I: 1 C: 2	I: 2 C: 0
Lua, 2015, Malaysia	I: 7 C: 4	I : 4 C: 4	I: 3 C: 0	None
Ishiwatari, 2016, Japan	I: 20 C: 19	I: 13 C: 11	I: 6 C: 4	I: 1 C: 4