

Original Article

## Rectal Indomethacin Prevents Moderate to Severe Post-ERCP Pancreatitis and Death and Should Be Used Before the Procedure: A Meta-Analysis of Aggregate Subgroup Data

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### Abstract

**Background:** Despite overall evidence in the literature favoring rectal indomethacin in preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), its role in preventing potentially fatal complications is not well explored.

**Method:** A comprehensive electronic literature search was done to select randomized controlled trials (RCTs) comparing rectal indomethacin and placebo in preventing PEP. Methodological quality was assessed using the Cochrane risk of bias tool. Statistical heterogeneity was characterized. Random effect model meta-analysis was used. Several subgroup, sensitivity and aggregate subgroup data analyses were completed based on specific risk factors or patient characteristics to identify patient populations who may benefit most from rectal indomethacin.

**Results:** A total of eight out of 336 trials published between 2007 and 2016 (n=3324) were included. Analysis showed administering rectal indomethacin before rather than during or after ERCP significantly reduced PEP rates (odds ratio (OR): 0.56 [0.40–0.79]). Rectal indomethacin also significantly decreased the rate of moderate to severe PEP and death amongst all patients (OR: 0.53 [0.31–0.89] and 0.10 [0.02–0.65], respectively). Rectal indomethacin significantly prevented PEP in patients with sphincter of Oddi dysfunction (SOD) (OR: 0.49 [0.30–0.78]) and those undergoing biliary sphincterotomy (OR: 0.63 [0.42–0.95]), but not in those undergoing precut or pancreatic sphincterotomy or prophylactic pancreatic stent placement. Sensitivity analysis showed that the effect remained significant after two studies with high risk of bias were excluded.

**Conclusion:** Rectal indomethacin significantly decreases the occurrence of moderate to severe PEP and death in all patients, only if given before the procedure.

**Key words:** *Meta-analysis; Post-ERCP pancreatitis; Prevention; Rectal indomethacin.*

Acute pancreatitis is the most common major post-endoscopic retrograde cholangiopancreatography (ERCP) complication. It ranges from 1% to 10% and as high as 25% to 30% in high-risk patients.

Risk factors include patient-related factors such as young age, female gender, pancreas divisum, sphincter of Oddi dysfunction (SOD), prior post-ERCP pancreatitis (PEP), and procedure-related factors

such as difficult cannulation and pancreatic duct injection (1–3). Multiple modalities have been proposed to decrease the rate of PEP, including technical improvement, prophylactic pancreatic stent and pharmacoprevention (4, 5). The list of pharmacological agents that have been proposed and tested for this purpose is long and varied (1, 6). Among all these, rectal indomethacin has gained universal attention after a large US-based multicentre double-blinded randomized controlled trial (RCT) in high-risk patients (7). The trial showed a significant risk reduction of 46% in those who received it. Later, in a meta-analysis of four randomized controlled trials, our group showed that rectal indomethacin significantly reduced the rate of PEP, including moderate to severe pancreatitis to half in both high-risk and low-risk patients (8). The latest recommendation from the European Society of Gastrointestinal Endoscopy advocates routine use of rectally administered diclofenac or indomethacin immediately before or after ERCP to prevent PEP (9). In the absence of direct comparison, a network meta-analysis showed that rectal nonsteroidal anti-inflammatory drugs (NSAIDs) were superior to pancreatic duct stenting and was not inferior to the combination of rectal indomethacin and prophylactic pancreatic stent placement for the prevention of PEP (10). Several other meta-analyses showed that rectal indomethacin or diclofenac reduced the overall rate of PEP and decreased both mild and moderate to severe PEP in both high-risk and unselected patients (8,11–18). However, more recent studies did not support previous findings especially in unselected patients (19, 20). Specifically, in the most recent double-blinded single centre RCT on 449 consecutive patients, rectal indomethacin had no significant effect on preventing PEP as compared to placebo (7.2% versus 4.9%;  $p=0.33$ ) (20). In the largest published RCT, pre-procedure rectal indomethacin was shown to be superior to risk-stratified post-procedural administration in high-risk patients (21).

Despite the significant number of studies including RCTs and systematic reviews, the effect of the intervention on major adverse events such as moderate to severe PEP and death is not well scrutinized. Therefore, we aimed to complete a more contemporary meta-analysis of aggregate subgroup data, including RCTs comparing rectal indomethacin and placebo in preventing more severe PEP and mortality.

## MATERIAL AND METHODS

### Trial selection criteria

Only RCTs were included. For inclusion, we required that patients undergoing ERCP in the trial have been randomized to rectal indomethacin or placebo. No studies were excluded based on the language of publication, quality of study, duration of follow-up or country of origin.

### Search strategy

Comprehensive computerized medical literature searches were conducted using OVID MEDLINE (1946 to May 2016),

EMBASE (1980 to May 2016), Cochrane library, clinical trials database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and ISI Web of knowledge from 1980 to May 2016. Other available sources (grey literature) were also searched through cross-referencing. Articles were selected using a highly sensitive search strategy to identify reports of RCTs, with a combination of MeSH headings and text words that included 1) Pancreatitis, 2) Indomethacin and 3) ERCP. Recursive searches and cross-referencing were carried out using a 'similar articles' function; bibliographies of the articles identified after an initial search were also manually reviewed. Non-randomized trials, studies with insufficient data on clinical response, abstracts, any study on rescue therapy, pediatric studies and duplicate publications were excluded. Data extraction and quality control were independently done by two reviewers (MY and MAA). A third reviewer (JM or ANB) was involved if conflict occurred. We first tried to extract the raw data from available published information. Corresponding authors were then contacted to obtain missing data, where appropriate. If missing data could not be obtained then the trial was excluded and the reason was described.

The risk of bias of the included studies was evaluated using the Cochrane Collaboration tool for assessing the risk of bias recommendations by the Cochrane Collaboration (22, 23). The study was registered (CRD42016038397) in PROSPERO (International prospective register of systematic reviews).

### Outcome measures

The main outcome of interest was the incidence of PEP within a 7-day period following the ERCP. Secondary outcomes were set to compare incidence of moderate to severe post-ERCP pancreatitis in the 7-day period following ERCP as well as death. Subgroup analyses and analyses of aggregate subgroup data were planned beforehand according to different patient characteristics that included high-risk versus average-risk for PEP; sphincter of Oddi dyskinesia; those undergoing pancreatic, biliary, or precut sphincterotomy or prophylactic pancreatic stent placement; and according to differing doses and timing of administration of rectal indomethacin. The analysis was also planned for the rate of moderate to severe pancreatitis and death. We respected authors' definition of high-risk and average-risk population as mentioned previously.

### Statistical analysis

Summary outcomes are described as proportions and 95% confidence intervals (CI). Pooled proportionate rates of PEP were calculated separately for rectal indomethacin and placebo and were reported as proportions and confidence intervals. A meta-analysis of intention-to-treat study-level or aggregate subgroup data was done using the random effect model Mantel-Haenszel method for each risk factor (24). Peto method was used when the rate of events was under 1% (24). The significance and extent of statistical heterogeneity were calculated

using the  $Q$  test and  $I^2$  index, respectively (23). Odds ratios (OR) were calculated for each analysis with the corresponding 95% confidence intervals. Number needed to treat (NNT) was calculated using the reciprocal of absolute risk difference rather than treat-as-one-trial method to avoid Simpson's paradox (25, 26). Funnel plots, Begg adjusted rank correlation test and the Egger regression asymmetry test were planned to detect the possibility of publication bias in meta-analyses including more than 10 studies (23, 27, 28). We also planned to perform meta-regression and sensitivity analyses based on the quality and weight of the trials (23). Sensitivity analyses were planned, excluding studies with high risk of bias and by excluding the largest trial.

All statistical analyses were done using RevMan (Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and R (version 2.13.0, R Foundation for Statistical Computing, Vienna, Austria, 2008). The PRISMA statement outline for reporting systematic reviews and meta-analyses was used to report on this work (29).

## RESULTS

### Characteristics of included trials

A total of eight out of 336 identified studies (N=3324 patients, including 1684 in treatment group and 1640 in placebo group) were included; all were performed between 2007 and 2016. All studies were published in English. There was no missed data, and the authors provided all required raw data not previously presented in published manuscript. Figure 1 depicts the PRISMA flow diagram. Table 1 shows the methodological and clinical details for each trial.

### Clinical heterogeneity

All trials used relatively similar criteria to define PEP as depicted in Table 1. Two studies included only high-risk patients (7, 30) while the rest included unselected patients (19, 20, 31–34). All included studies used 100 mg of rectal indomethacin. Five studies administered pre-procedure rectal indomethacin (19, 31–34), one intra-procedure (20) and two post-procedure (7, 30). Three studies allowed prophylactic pancreatic stent (7, 20, 34) but three did not (19,30,31) and two studies were unclear in regard to this possible co-intervention (32, 33).

### Risk of bias

Figure 2 presents the consensus risk of bias assessments of the included studies. Risk of bias was low in all but two studies (33,34).

### Publication bias

A funnel plot was not provided since the number of included studies was fewer than 10, and in this case, the power of the

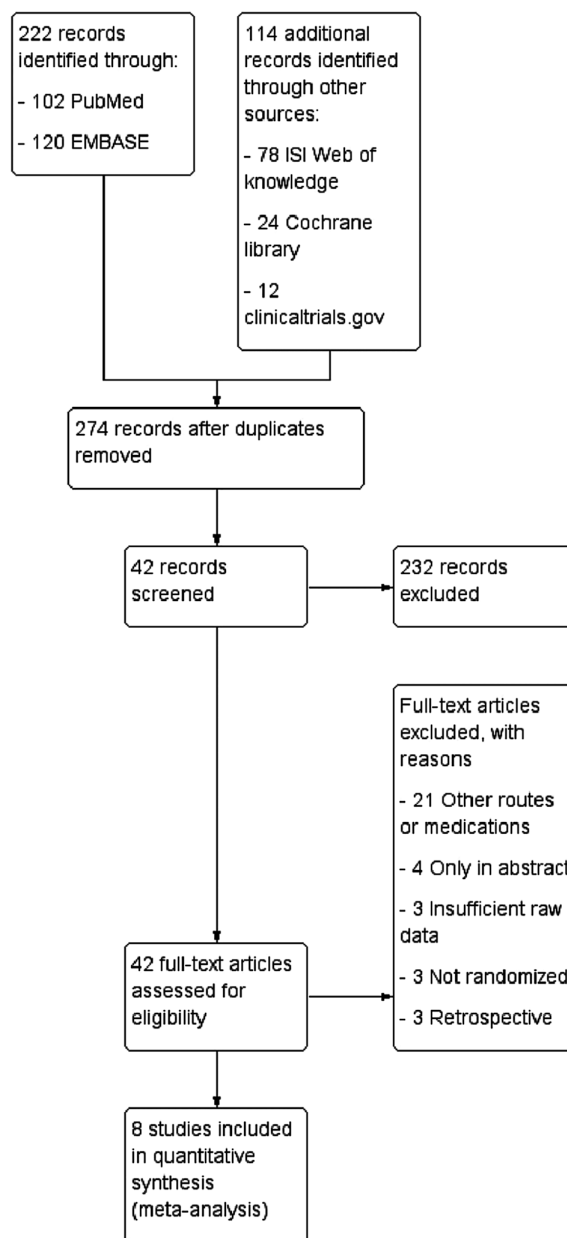


Figure 1. PRISMA flow diagram of included and excluded trials.

tests is considered too low to distinguish chance from real asymmetry according to recommendation by the Cochrane Collaboration (23).

### Analysis of main outcome

All included studies reported the primary outcome. The pooled proportion estimates of PEP were 5.6 (95% CI: 4.5–11.5) with rectal indomethacin and 8.8 (95% CI: 7.5–14.4) with placebo. This rate was significantly lower with rectal indomethacin as compared to placebo (OR=0.56 [0.39–0.82]). Statistical heterogeneity was significant ( $p$ : 0.07,  $I^2$ : 46%). The number needed to treat was 20. We were unable to perform a separate meta-regression analysis since the number of included studies

**Table 1.** Characteristics of included studies. PEP: Post-ERCP pancreatitis

Study	Year	Country	Number of patients	Number of post-ERCP pancreatitis	Intervention (Indomethacin 100 mg per rectum)	Definition of PEP
Andrade-Dávila (30)	2015	Mexico	166	21	After ERCP	Pain, lipase or amylase > x3, positive imaging
Dobronte et al (33)	2012	Hungary	228	22	10 Minutes before ERCP	Clinical/Amylase > x3/ prolonged hospital admission
Dobronte et al (19)	2014	Hungary	686	22	10–15 minutes before ERCP	Clinical/Amylase 24h
Elmunzer et al (7)	2012	USA	602	79	Immediately after ERCP	Pain, Amylase > x3, admission for at least 2 nights
Levenick et al (20)	2016	USA	449	27	during ERCP	Pain, lipase > x3, admission >2 nights
Montaño Loza et al (34)	2007	Mexico	150	16	2 hours before ERCP	Clinical, amylase level
Patai et al (32)	2015	Hungary	574	55	Within one hour before ERCP	Pain, amylase > x3, admission >2 nights
Sotoudehmanesh et al (31)	2007	Iran	490	22	right before ERCP	Pain, Amylase > x3, admission >2 days

was less than 10 (23). Figure 3 depicts the Forest plots of the selected study analyses.

### Subgroup analyses

Meta-analysis of aggregate subgroup data on risk factors

Table 2 represents the detail of these analyses. In summary, rectal indomethacin significantly decreased the rate of moderate to severe PEP. Death happened only and more significantly with placebo (five out of 177 events) and not with indomethacin (zero out of 107 events). The effect remained statistically significant in sensitivity analysis after using the total number of patients instead of the ones with PEP as denominator. It also significantly decreased the rate of PEP amongst subgroup of patients with sphincter of Oddi dysfunction (SOD). The effect remained robust in sensitivity analysis after excluding the largest SOD population from one study (7). Rectal indomethacin was also significantly effective in preventing PEP in those patients undergoing biliary sphincterotomy. This effect was not significant after excluding two studies on high-risk population (OR:0.69 [0.42–1.15]). It did not significantly decrease the rate of PEP amongst subgroup of patients who received a pancreatic sphincterotomy, precut sphincterotomy, or prophylactic pancreatic stent.

#### Timing of dosing

Amongst five studies (n=2107) administering pre-procedure suppositories (19, 31–34), the difference remained statistically significant (OR: 0.56 [0.40–0.79],  $p=0.0008$ ), favoring rectal indomethacin. All included patients were randomized

regardless of the risk for post-ERCP pancreatitis. There was no statistically significant heterogeneity in this analysis ( $I^2$ : 0%). Rectal indomethacin was not statistically superior to placebo when analyzing three studies (n=1217) using intra- or post-procedure dosing (OR: 0.56 [0.21–1.49],  $p=0.25$ ) (7, 20, 30). There was statistically significant heterogeneity in this analysis ( $p$ : 0.009,  $I^2$ : 79%).

#### High-risk versus unselected patients

After excluding the two studies on high-risk populations (7, 30), the PEP rates were no longer statistically different (OR: 0.65 [0.42–1.00]). There was statistically significant heterogeneity in this analysis ( $p$ : 0.12,  $I^2$ : 43%). The OR for the rate of PEP was 0.37 (0.16–0.84) and significant for rectal indomethacin amongst the two studies (n=768) exclusively done in high-risk patients. Number needed to treat was 10. There was no statistically significant heterogeneity in this analysis ( $p$ : 0.16,  $I^2$ : 50%).

### Sensitivity analyses

The effect remained significant when two studies with high risk of bias (33, 34) were excluded (OR: 0.57 [0.37–0.89]) or after excluding the largest included trial (7) (OR: 0.52 [0.35–0.79]).

## Discussion

To our knowledge, this is the first meta-analysis of aggregate subgroup data on the role of rectal indomethacin in preventing moderate to severe post-ERCP pancreatitis and mortality. We

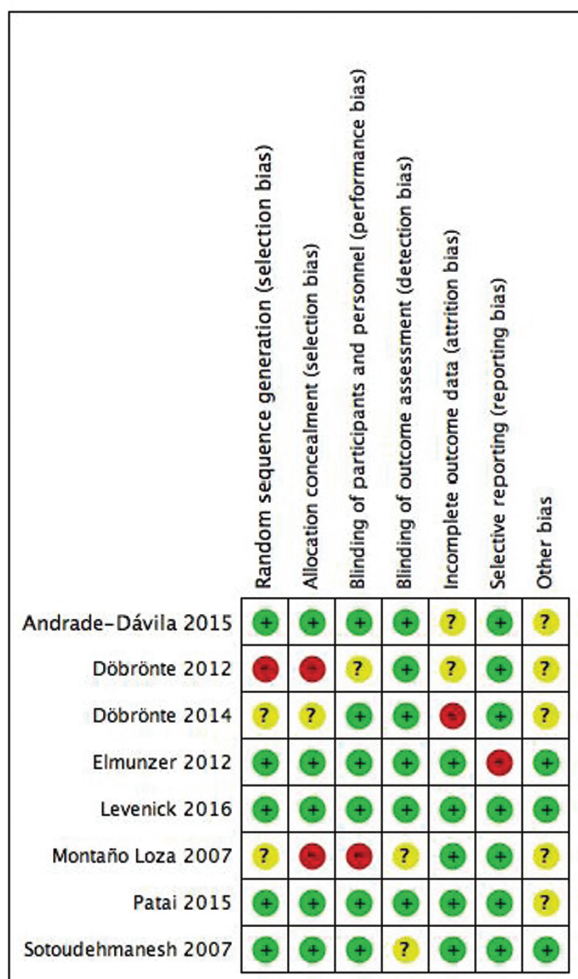
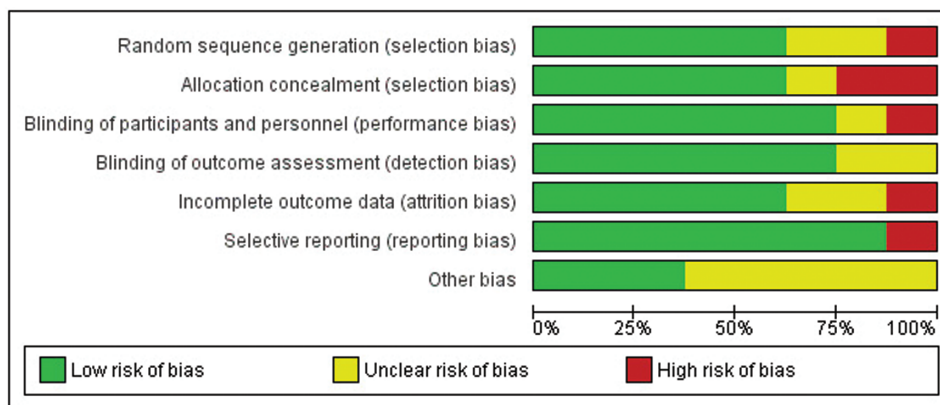


Figure 2. Consensus risk of bias assessments of the included studies. Green: Low risk, Yellow: Unclear, Red: High risk.

used aggregate data from the different trials and performed a meta-analysis in each subgroup according to PEP-risk category. Our study tried to answer important questions that have remained unanswered despite multiple clinical and meta-analytical studies on this topic using the additional statistical power brought about by summary analyses of clinically pertinent patient subgroups. Our study identifies population subgroups

that also benefit from this approach, mainly in patients with sphincter of Oddi dyskinesia. The intervention effectively decreases the rate of moderate to severe post-ERCP pancreatitis and fatality in all patients, regardless of patient risk category. Also, pre-procedure dosing appears to be significantly more effective than post-procedure administration of rectal indomethacin in preventing PEP.

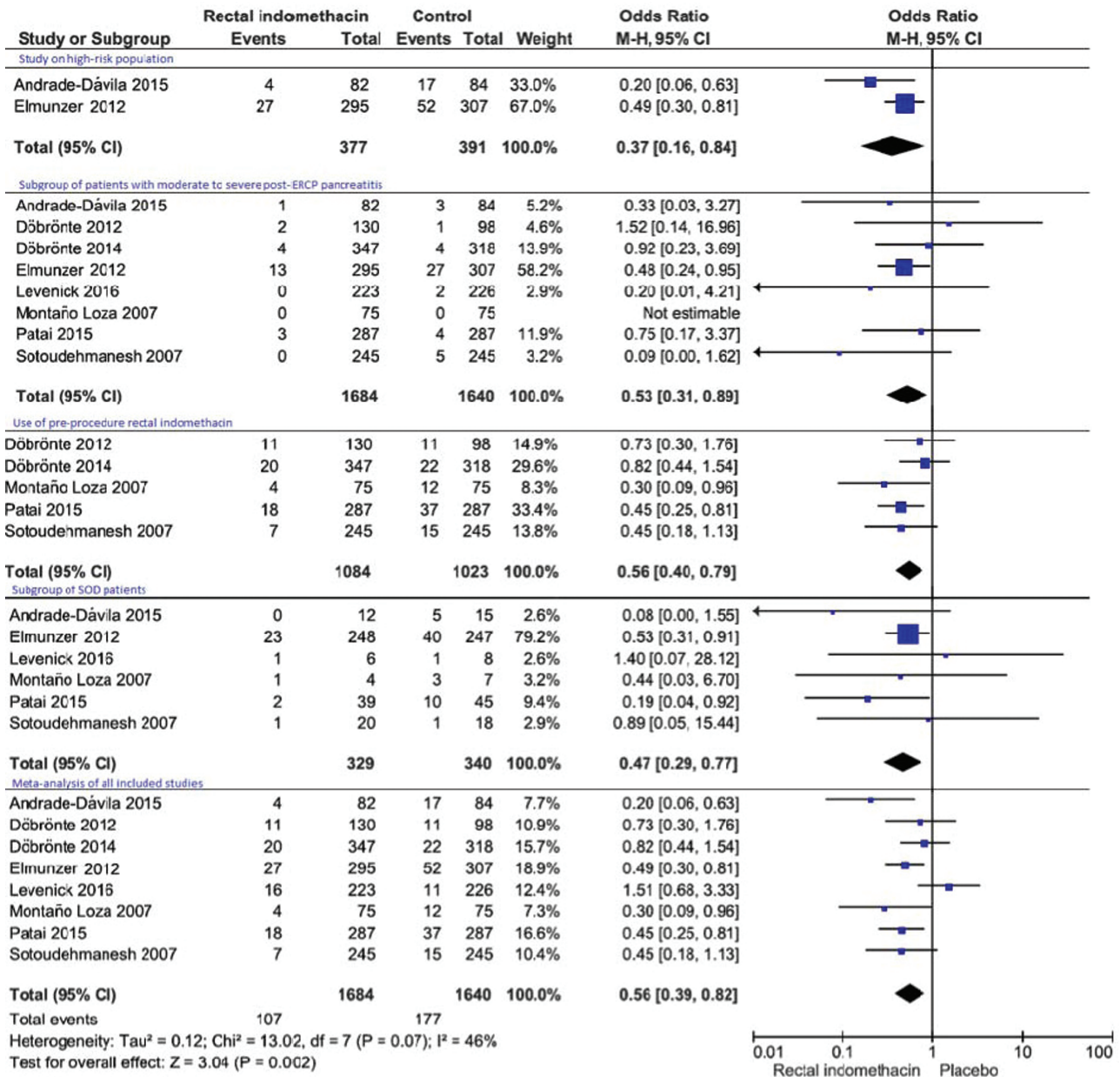


Figure 3. Forest plot of selected Mantel-Haenszel meta-analysis of the post-ERCP pancreatitis with rectal indomethacin versus placebo. *CI*, confidence interval; *M-H*, Mantel-Haenszel.

Our sensitivity analyses show results that remain unchanged when excluding the study with high risk of bias or with the largest sample size. All but one of the included studies demonstrated at least an arithmetical trend favoring rectal indomethacin. Despite the observed statistical heterogeneity in some of the analyses, the designs of the included RCTs were very similar, thereby resulting in low clinical heterogeneity, not measurable by statistical means, which might further enhance the validity of the findings. Some of the possible reason for heterogeneity in subgroup analyses might be the timing of administration of rectal indomethacin, difference in patient population regarding the risk for PEP and considering cumulative outcome by combining mild, moderate and severe PEP. Based on our aggregate

subgroup meta-analyses, there was no more heterogeneity when we stratified the data based on those factors.

We showed rectal indomethacin is effective in preventing PEP in patients at high-risk for it. This is consistent with the results of the two large RCTs performed exclusively on high-risk patients. Our meta-analysis of aggregate subgroup data from five studies showed that SOD patients particularly benefited from the intervention. Minimal heterogeneity was found in this analysis. A large US study (7), which mainly included SOD patients, concluded that rectal indomethacin significantly decreased the rate of PEP in included patients with a NNT of 12, which was close to the NNT achieved for SOD patients in our study, as depicted in Table 2. Based on the grade of the

**Table 2.** Meta-analysis of aggregate subgroup data in each risk category. OR: Odds Ratio; CI: Confidence Interval; NNT: Number Needed to Treat; NA: Non-applicable

Subgroup analyses	Number of patients	OR	CI 95%	Heterogeneity (I <sup>2</sup> )	NNT
Preventing moderate to severe PEP (7, 19, 20, 30–34)	3324	0.53	0.31–0.89	0%	100
Sphincter of Oddi Dyskinesia (7, 19, 20, 30–34)	694	0.49	0.30–0.78	0%	10
Death	284 with post-ERCP pancreatitis	0.10	0.02–0.65	0%	NA
	3324 randomized patients	0.13	0.02–0.77	0%	NA
Biliary sphincterotomy (7, 19, 20, 31–34)	2062	0.63	0.42–0.95	53%	33
Pancreatic sphincterotomy (7, 19, 20, 30–34)	492	0.81	0.36–1.83	34%	NA
Precut sphincterotomy (7, 19, 20, 30–34)	436	0.50	0.14–1.82	72%	NA
Prophylactic pancreatic stent (7, 19, 20, 30–34)	572	0.98	0.26–3.62	72%	NA

evidence, we strongly recommend administering rectal indomethacin in all patients suspected of SOD undergoing ERCP.

Stent placement in the pancreatic duct has been one of the proven effective interventions for post-ERCP pancreatitis prophylaxis associated with a protective OR of 0.44 (0.24–0.81) (35–37); however, more than 20% of endoscopists do not perform prophylactic pancreatic stenting (37). The combination of rectal indomethacin and prophylactic pancreatic stent placement in the current meta-analysis does not significantly alter the rate of PEP compared to rectal indomethacin alone. This is the first meta-analytic evidence showing lack of synergistic protection of rectal indomethacin and pancreatic stenting. A post-hoc analysis by Elmunzer et al. has previously shown a higher PEP rate following this combination compared to rectal indomethacin alone (9.7% versus 6.3%, respectively) (38). Moreover, their economic model demonstrated rectal indomethacin alone is more cost-effective than placebo, prophylactic pancreatic duct stent placement, or a combination of rectal indomethacin and stent placement (38). A network meta-analysis, based on indirect comparisons, has concluded that rectal NSAIDs are superior to prophylactic pancreatic stent placement (OR: 0.48 [0.26–0.87]), and a combination of rectal NSAIDs and prophylactic pancreatic stent placement is not superior to rectal NSAIDs (OR: 1.46 [0.79–2.69]) (39). Only the advent of true head-to-head data will provide more definitive clarity on this issue, and we await the results from at least two ongoing RCTs (40). However, to date, there is insufficient proof to recommend the combination of these two modalities over performing either.

In our meta-analysis of aggregate subgroup data, rectal indomethacin significantly decreases the rate of moderate to severe PEP, as well as the rate of death from ERCP or post-ERCP pancreatitis in all patients. This alone may be an indication for universal routine administration since the majority of morbidity

and mortality due to PEP occurs in patients with moderate to severe cases (41).

We have shown that pre-procedural administration of rectal indomethacin appears to be superior to intra- or post-procedure administration, a result no doubt driven statistically by the findings of a very recent large RCT from China on 2600 unselected patients undergoing ERCP. In this trial, patients were randomized to either pre-procedure rectal indomethacin or risk-stratified post-procedural administration in high-risk patients (21). Post-ERCP pancreatitis occurred significantly less in patients who universally received pre-procedural rectal indomethacin (4% versus 8% respectively,  $p < 0.0001$ ). There might exist a biologically plausible explanation for this effect. Indeed, peak plasma concentrations are achieved in 30 minutes following rectal administration of indomethacin (42). Therefore, post-ERCP dosing may theoretically render the NSAID not available at the time of the initial injury to the pancreas and thus less able to prevent the inflammatory cascade. It may be prudent to administer rectal indomethacin, when indicated, before the procedure rather than during or after ERCP in patients without a contraindication.

Although meta-analyses have been described to provide high quality evidence for clinical use, they are not free of risk of bias. The possibility of missed trials cannot be completely ruled out. We tried to minimize this possibility by including several types of publications, search methods and all languages. However, the number of included studies was not sufficient to perform a meta-regression analysis in a search for causes of statistical heterogeneity.

In conclusion, this meta-analysis suggests rectal indomethacin is effective in preventing post-ERCP pancreatitis and that this protective effect is true for high-risk patients, specifically in those with sphincter of Oddi dyskinesia. It also significantly decreases the rate of moderate to severe PEP and death

in unselected patients, and this should be given to all patients without a contraindication prior to the ERCP.

#### Registration & Funding

This study was registered (CRD42016038397) in PROSPERO (International prospective register of systematic reviews). The authors received no funding to support this study.

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#### Conflicts of Interest

Dr Yaghoobi is supported by an Internal Medicine Career Award by the department of medicine at McMaster University.

#### Author Contributions

MY and ANB: conception and design, or analysis and interpretation of data. MY, MAA, JM, MM and ANB: drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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