



Rectal indomethacin for the prevention of post-ERCP pancreatitis: A meta-analysis of randomized controlled trials

BILIARY/PANCREATIC

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ABSTRACT

Background/Aims: This meta-analysis was undertaken to evaluate the effect of rectal indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

Materials and Methods: Major databases including Embase, Medline, Science Citation Index Expanded, Pubmed and the Cochrane Central Register of Controlled Trials, were searched to identify all relevant studies from January 1960 to July 2013. Randomized controlled trials (RCTs) comparing prophylactic use of rectal indomethacin versus placebo were included. Risk ratio (RR) with 95% confidence interval (CI) was calculated using fixed- or random-effect models.

Results: Three studies met the inclusion criteria and were included in the final analyses. The overall incidence of post-ERCP pancreatitis (PEP) was significantly decreased by prophylactic rectal indomethacin compared with the placebo (RR=0.51; 95% CI=0.37-0.70). The pooled incidence of moderate to severe pancreatitis was also decreased by rectal indomethacin prophylaxis (RR=0.43; 95% CI=0.23-0.80).

Conclusion: Rectal indomethacin can reduce the overall incidence and the severity of PEP.

Keywords: Endoscopic retrograde cholangiopancreatography, indomethacin, meta-analysis, post-ERCP pancreatitis, prophylaxis

INTRODUCTION

Acute pancreatitis is the commonest complication of post-endoscopic retrograde cholangiopancreatography (ERCP). In the majority of patients the incidence of post-ERCP pancreatitis (PEP) varies from 1% to 10%, but may reach 30% in high-risk cases (1). The variation in this incidence is mostly due to the heterogeneous interaction of patient and procedure-related factors (2). Several endoscopic interventions and pharmacologic agents have been studied in the prevention of PEP. Pancreatic duct stenting greatly decreased the incidence of PEP in high-risk patients (3), but it is not convenient because of highly technical requirements and restricted selection of patients. Therefore, effective pharmacologic agents remain attractive.

Indomethacin is safe, inexpensive, easily administered, and widely available. In experimental acute pancreati-

tis models, indomethacin was shown to attenuate the severity and lower the mortality (4-6). Other studies undertaken around the same time, however, showed no beneficial effect (7-8). Data from recent clinical trials suggest that indomethacin had a protective effect against PEP (9). In this study, we sought to systematically evaluate the existing evidence of rectal indomethacin prophylaxis for the prevention of PEP.

MATERIALS AND METHODS

Literature search

A comprehensive literature search of Embase, Medline, Science Citation Index Expanded, Pubmed and the Cochrane Central Register of Controlled Trials in the Cochrane Library was performed for studies from January 1960 to July 2013. Medical subject headings and

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keywords were as follows: ("endoscopic retrograde cholangiopancreatography" or "ERCP" or "post-ERCP pancreatitis" or "pancreatitis" or "PEP") AND ("indomethacin" or "nonsteroidal anti-inflammatory drugs" or "NSAIDs"). Combinations of words and different styles of the search terms were used. Relevant papers were identified from the reference lists of previous papers. Only Randomized controlled trials (RCTs) with full-text descriptions were included. The final inclusion of articles was determined by two authors (N.S. and L.D.); when this failed, the third author (K.A.) adjudicated. All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Inclusion and exclusion criteria

Two authors (N.S. and L.D.) independently identified and screened studies that can meet the requirements.

Inclusion criteria:

1. The diagnosis of PEP was defined according to consensus criteria (10).
2. RCTs comparing prophylactic rectal indomethacin versus placebo.
3. Main outcomes are defined as the incidence of PEP.
4. English language articles published as full text articles.

Exclusion criteria:

1. Abstracts, editorials, letters, reviews, expert opinions, and case reports.
2. Studies without outcome measures.

Data extraction and quality assessment

Two independent observers (W.H. and P.X.) extracted the data. The recorded data included the number of patients, population characteristics, administration of drugs, outcomes, and any adverse effects of therapy. The quality of the included studies was assessed independently by two reviewers using the Modified Jadad score (11). A third reviewer (K.A.) was available to resolve any disagreement by consensus and discussion.

Statistical analysis

The meta-analysis was executed using Review Manager V 5.0 software (provided by the Cochrane Collaboration, Oxford, UK). The statistical method was referred to the Cochrane Handbook for Systematic Review of Intervention. Heterogeneity among the studies was evaluated using Cochran's χ^2 test and a p value of less than 0.05 was considered significantly different (12). I^2 statistics were used to measure the percentage of total variation across the studies (an I^2 of 50% or more indicating the presence of heterogeneity). The meta-analysis was analyzed using a fixed-effect model if there was no homogeneity among the studies, and otherwise the random effects were performed (13). The pooled outcomes were shown in a forest plot and reported as Mantel-Haenszel relative risk (RR) with a corresponding 95% confidence interval (CI).

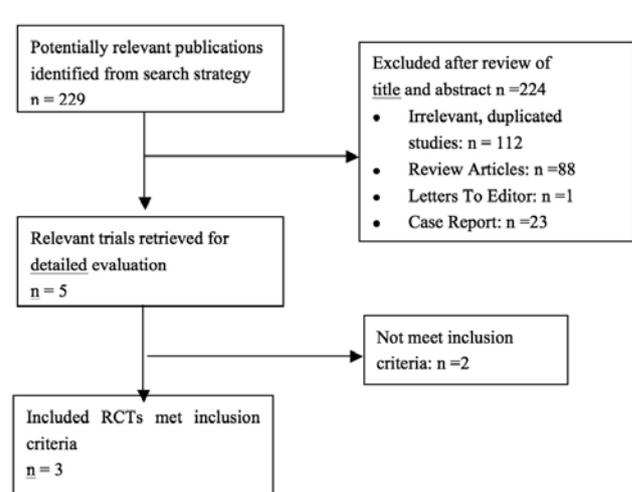


Figure 1. Flow diagram illustrating the process of study identification. n, numbers.

RESULTS

Study selection and quality assessment

Details of the selection of RCTs are shown in Figure 1. After initial screening, five relevant prospective studies were identified for evaluation in details (14-18). Two studies were excluded because full texts in English were not retrieved (17-18). Finally, three studies involving a total of 1242 patients were included for data extraction (14-16). Except for one single-center study, two studies were designed as multicenter. Although all three studies were randomly selected, only two of them described the appropriate method of randomization and allocation concealment of randomization. Two studies were appropriately double-blinded, and described as withdrawals and dropouts. The study quality assessment is shown in Table 1.

Patient characteristics

Basic characteristics of the patients are shown in Table 2. Of the 1242 patients included, 615 received rectal indomethacin and 627 were given the placebo. Endoscopic interventions, (sphincterotomy, pancreatic stent, etc.) were given to patients during the procedure if required.

Meta-analysis results

Results of the meta-analysis are reported as Mantel-Haenszel RR with 95% CI and shown in Figures 2 and 3.

The overall incidence of PEP was 7.64% (47 of 615 patients) in the indomethacin group and 15.15% (95 of 627 patients) in the placebo group. There was a significant difference in the incidence of PEP between the two groups (RR=0.51; 95% CI=0.37–0.70; $p<0.0001$). These three studies were not significantly heterogeneous ($\chi^2=0.21$ $p=0.90$; $I^2=0\%$).

Moderate to severe PEP was reported in 45 patients, 2.1% (13/615) of whom were in the indomethacin group and 5.1% (32/627) in the control group (Figure 3). The incidence of mod-

Table 1. Characteristics of studies and quality assessment

Trials	Year	Country	Setting	Patients (n)	Randomization	Description of allocation concealment	Blinding	Description of withdrawals and dropouts	Modified Jadad score
Elmunzer et al. (14)	2012	The United States	Multicenter	602	Appropriate randomization	Yes	Appropriate double-blind	Yes	7
Montano et al. (15)	2007	Mexico	Multicenter	150	Randomization	NA	Single-blind	NA	1
Sotoudehmanesh et al. (16)	2007	Iran	Single center	490	Appropriate randomization	Yes	Appropriate double-blind	Yes	7

NA: not available.

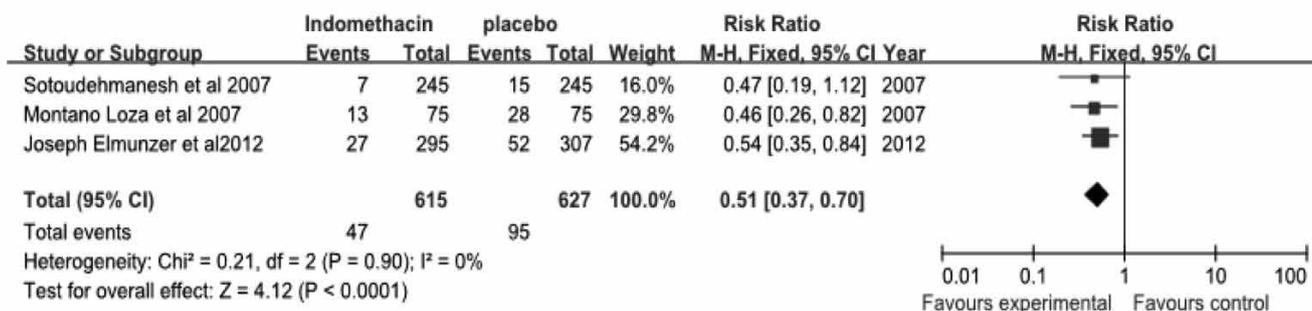


Figure 2. Forest plot demonstrating a significant decrease in the overall incidence of post-ERCP pancreatitis by rectal indomethacin prophylaxis. CI, confidence interval; M-H, Mantel-Haenszel.

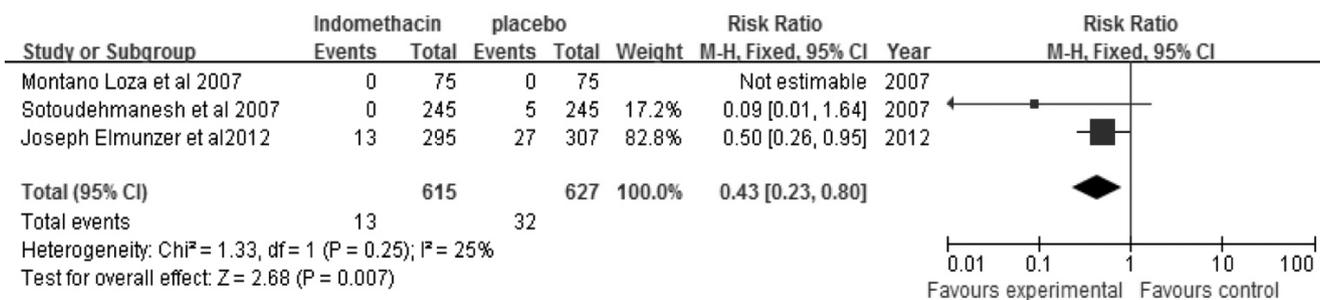


Figure 3. Forest plot demonstrating a significant decrease in the incidence of moderate to severe post-ERCP pancreatitis by rectal indomethacin prophylaxis. CI, confidence interval; M-H, Mantel-Haenszel.

erate-to-severe PEP was significantly reduced by prophylactic indomethacin administration (RR=0.43; 95% CI=0.23-0.80; p=0.007). There was no significant heterogeneity among the studies (χ²=1.33, p=0.25; I²=25%).

No mortality was reported in all three studies. Thirteen adverse events, which were potentially attributable to the study intervention, were reported in one study (14): clinically significant bleeding occurred in 11 patients (four in the indomethacin group and seven in the placebo group); two cases of acute renal failure in the placebo group (Table 2).

DISCUSSION

The prevention of PEP remains an ongoing area of active research. A large number of endoscopic interventions and pharmacologic agents have been studied for the prevention of PEP however, their effects are often disappointing.

Although great decreases in the incidence of PEP have been shown by pancreatic stents in high risk patients, these studies, however, are heterogeneous in study design and characteristics of the stent and may draw definitive conclusions (3,19-20). Moreover, the placement of a stent is expensive and requires an experienced endoscopist for an appropriate insertion. Therefore, effective pharmacologic agents are preferable.

Drugs used to prevent PEP are commonly divided as sphincter relaxants, anti-secretory agents, protease inhibitors, anti-inflammatory agents, anti-oxidants, etc. The rationale of non-steroid anti-inflammatory drugs (NSAIDs) for PEP is based on its ability to inhibit inflammatory substances in the early phase of pancreatitis, such as prostaglandins, phospholipase A2, and a neutrophil-endothelial interaction (21). Three meta-analyses demonstrated a decrease in of the incidence of PEP with the use of rectal NSAIDs with no adverse side-effects (22-24). Ding

Table 2. Basic characteristics of the patients after comparing the efficacy of indomethacin with that of the placebo for the prevention of post-ERCP pancreatitis

Trials	Intervention	Patients	Age (year) (mean±SD)	Male/Female	SOD, n (%)	Sphincterotomy, n (%)	Moderate or Pancreatic stent, n (%)	PEP, n (%)	severe PEP, n (%)	Adverse Events
Elmunzer et al. (14)	100 mg of indomethacin immediately after ERCP	295	44.4±13.5	66/229	155 (52.5)	172 (58.3)	246 (83.4)	27 (9.2)	13 (4.4)	Bleeding 4,
	Placebo	307	46.0±13.1	60/247	160 (52.1)	170 (55.4)	250 (81.4)	52 (16.9)	27 (8.8)	Bleeding 7, ARF 2
Montano et al. (15)	100 mg of indomethacin 2 h before ERCP	75	55.37±18.0	26/49	NA	11 (39.5)	15 (20)	4 (5.3)	0	0
	Placebo	75	51.1±17.0	24/51	NA	25 (49)	8 (10.7)	12 (16)	0	0
Sotoudehmanesh et al. (16)	100 mg of indomethacin immediately before ERCP	245	58.4±17.1	111/134	19 (7.8)	138 (56.3)	No	7 (3.2)	0	0
	Placebo	245	58.1±16.8	115/130	17 (6.9)	128 (52.2)	No	15 (6.8)	5 (2.3)	0

ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; SOD, sphincter of Oddi dysfunction; ARF, acute renal failure; NA, not available.

et al. (25) conducted an updated and comprehensive meta-analysis on NSAIDs in preventing PEP, in which data from the latest trials were also included. However, there were certain limitations to that study: 1) different type and the route of administration for the NSAIDs were not stratified, 2) pancreatic stenting was inconsistently used, 3) low-quality studies were included, and 4) the study was heterogeneous.

Indomethacin, an NSAID, is easily available, inexpensive and easy to administer, making it ideal for prophylaxis. This meta-analysis of three RCTs enrolling 1242 patients showed that the overall incidence of PEP correlates with the prophylactic use of rectal indomethacin (RR=0.51; 95% CI=0.37-0.70; $p<0.0001$). In the subgroup analysis, the incidence of moderate to severe PEP we also decreased by prophylactic rectal indomethacin (RR=0.43; 95% CI=0.23-0.80; $p=0.007$). These results show a positive effect of prophylactic rectal indomethacin against PEP and the severe PEP. Our findings are similar to those of previous meta-analyses published on this topic (22-26). Particularly, we focused on indomethacin prophylaxis involving rectal administration, which provides a more specific answer to the question, rather than pooling all the NSAIDs together.

Most of the patients has good prognosis. There was no death in the studies. Only one study described the occurrence of adverse events, which did not show a definite association with rectal indomethacin (14). These results suggest that rectal indomethacin is a safe approach.

The diagnosis of PEP was made according to same criteria that serum amylase reached three times of upper limit of that observed in normal and pancreatitis-like abdominal pain. Three RCTs adopted the same intervention that one dose of 100 mg of rectal indomethacin was given immediately before or after

ERCP. All three trials are insignificant and heterogeneous, therefore, the results of this meta-analysis would be reliable.

This meta-analysis has limitations. First, there's unavoidable language bias, because two non-English studies were excluded. Secondly, one multicenter, randomized, placebo-controlled, single-blinded trial did not describe the allocation concealment of randomization, and withdrawals and dropouts, which may affect the overall quality of the meta-analysis.

In conclusion, rectal indomethacin could significantly decrease the overall incidence and the severity of PEP. When considering the costs, risks, and potential benefits, rectal indomethacin prophylaxis is recommended for the prevention of PEP, especially in high-risk patients.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Q.X., L.D.; Design - Q.X., L.D.; Supervision - Q.X.; Resource - K.A., L.D.; Materials - N.S., K.A., L.D.; Data Collection &/or Processing - N.S., K.A., L.D.; Analysis &/or Interpretation - Q.X., P.X., W.H., L.D.; Literature Search - N.S., K.A., L.D.; Writing - N.S., K.A., L.D.; Critical Reviews - Q.X., K.A., L.D.

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