Simple pharmacological prophylaxis for post-ERCP pancreatitis

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Pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP) is a serious complication that, at the minimum, prolongs hospital stay and, in rare cases, causes serious morbidity and death.[1] The potential for risk reduction through pharmacological prophylaxis has therefore been the subject of extensive investigation. Published data generally support the use of rectal indometacin to reduce the risk of post-ERCP pancreatitis.[2–4] However, studies on this topic differentiate themselves on two clinically relevant fronts: the timing of indometacin administration (before *vs* after the ERCP procedure), and patient selection (administration to all patients provided no contraindications to non-steroidal anti-inflammatory drugs [NSAIDs] *vs* administration only to patients at high risk of post-ERCP pancreatitis).

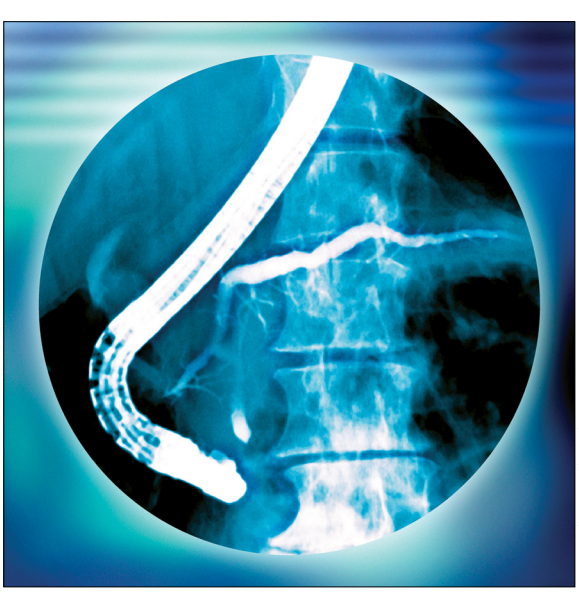
In *The Lancet*, Hui Luo and colleagues[5] present a comparison of pre-procedural rectal indometacin, administered to all patients, with post-procedural rectal indometacin, administered only to patients at high risk of post-ERCP pancreatitis. The first intervention is appealing in its pragmatism and potential to simplify the approach to pharmacological risk reduction in this population. The second intervention is widely known on the basis of Elmunzer and colleagues' influential study from 2012.[6]

Luo and colleagues[5] noted a lower risk of post-ERCP pancreatitis with routine pre-procedural indometacin (47 [4%] of 1297 patients) than with post-procedural risk-stratified administration (100 [8%] of 1303 patients; relative risk 0·47, 95% CI 0·34–0·66, p<0·0001). Among the subgroup of patients at high risk of post-ERCP pancreatitis, all receiving peri-procedural indometacin, a lower frequency of post-ERCP pancreatitis was observed with administration before ERCP as opposed to afterwards. Furthermore, among average-risk patients (roughly three-quarters of those enrolled in this study), indometacin before ERCP was better than no peri-procedural indometacin. Finally, although the trial was not powered to compare the frequency of gastrointestinal bleeding, there was no clinically meaningful difference in this secondary outcome between routine and selective administration of indometacin (13 [1%] of 1297 patients *vs* ten [1%] of 1303 patients).

The results from this trial should be framed in the context of its patient selection criteria and setting. Patients included in the trial were adults who underwent a diagnostic or therapeutic ERCP between Dec 15, 2013, and Sept 21, 2015, at six tertiary-care hospitals in China. The results do not apply to patients with a known pancreatic head mass, previous biliary sphincterotomy, previous NSAID use within 7 days, contraindication to NSAIDs (including allergy, gastrointestinal haemorrhage within 4 weeks, or renal dysfunction with serum creatinine >120 μmol/L), presence of coagulopathy or receipt of anticoagulation therapy within 3 days, acute pancreatitis within 3 days, or ERCP for biliary stent removal or exchange.

The results should also be considered in the context of existing evidence. Although most data support a benefit of indometacin for prophylaxis of post-ERCP pancreatitis, differences in patient selection and endoscopic interventions could explain some of the discrepancy between different studies; for example, findings from two recent trials showed no benefit for peri-procedural indometacin compared with placebo.[7,8]

Going forward, further investigations should seek to clarify the external validity of the results presented in this trial, particularly because more than 50% of patients were excluded before randomisation. For instance, a Canadian trial currently recruiting patients should offer further insight into the comparison of pre-procedural and post-procedural indometacin for prophylaxis of pancreatitis (NCT02111707). Analysis of large registries or administrative health data might also



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provide more generalisable estimates of the relative risk of post-ERCP pancreatitis and adverse events such as serious gastrointestinal bleeding. Importantly, large study samples would also allow for identification of patient subgroups in whom indometacin before ERCP is not beneficial.

In summary, Luo and colleagues have presented robust data supporting a new standard in pharmacological prophylaxis of post-ERCP pancreatitis: 100 mg of rectal indometacin administered 30 min before ERCP for all patients, excluding those with a known pancreatic head mass, contraindications to NSAIDs, recent NSAIDs, previous sphincterotomy, previous biliary stent, or recent pancreatitis.

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I declare no competing interests.

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Can biomarkers balance stroke and bleeding risk?

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Age and previous stroke, together with other clinical risk factors (often summarised in the CHA_2DS_2VASc score), identify patients with atrial fibrillation at high risk for stroke. Dose-adjusted warfarin prevents ischaemic strokes, prolongs life, and maintains autonomy in such patients.[1,2] Hence, oral anticoagulation is currently recommended for all patients with atrial fibrillation with two of the CHA_2DS_2VASc risk factors, and should be considered in those with one of them.[1,2] Although even reinitiation of anticoagulation after an intracerebral bleed seems to be associated with improved outcomes,[3,4] bleeding is a major reason to stop anticoagulation, which still drives underuse of anticoagulation in patients with atrial fibrillation.

Biomarkers have been studied as markers for stroke and bleeding outcomes in atrial fibrillation for several years.[5] In this issue of *The Lancet*, Ziad Hijazi and colleagues[6] report a comprehensive analysis of clinical parameters and blood biomarkers that are associated with bleeding events in anticoagulated patients with atrial fibrillation. The analysis for derivation was done in 14 537 patients with atrial fibrillation who were randomly assigned to apixaban versus warfarin in the ARISTOTLE trial and externally validated their findings in 8468 patients randomly assigned to dabigatran versus warfarin in the RE-LY trial.[7] Several blood biomarkers—most notably increased growth differentiation factor-15 (GDF-15), increased high-sensitivity cardiac troponin T (cTnT-hs), and low haemoglobin (or haematocrit) were independently associated with bleeding events. These associations were stronger than the associations with most clinical parameters tested. The authors constructed and validated a score based on a small set of factors with a strong association to bleeding events, comprising age, three biomarkers (GDF-15, cTnT-hs, and haemoglobin), and clinical history of previous bleeding ("the ABC-bleeding score"). The ABC-bleeding score yielded a higher c-index than did the HAS-BLED and ORBIT scores for major bleeding in both the derivation cohort (0·68 [95% CI 0·66–0·70] *vs* 0·61 [0·59–0·63] *vs* 0·65 [0·62–0·67], respectively) and in the external validation cohort (0·71 [95% CI 0·68–0·73] *vs* 0·62 [0·59–0·64] for HAS-BLED *vs* 0·68 [0·65–0·70] for ORBIT). A comparable score for stroke, proposed by the same research team called the "ABC-stroke score" (albeit using age and the biomarkers cTnT-hs and NT-proBNP, and a history of stroke rather than bleeding), predicts

Routine pre-procedural rectal indometacin versus selective post-procedural rectal indometacin to prevent pancreatitis in patients undergoing endoscopic retrograde cholangiopancreatography: a multicentre, single-blinded, randomised controlled trial

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Summary

Background Rectal indometacin decreases the occurrence of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). However, the population most at risk and the optimal timing of administration require further investigation. We aimed to assess whether pre-procedural administration of rectal indometacin in all patients is more effective than post-procedural use in only high-risk patients to prevent post-ERCP pancreatitis.

Methods We did a multicentre, single-blinded, randomised controlled trial at six centres in China. Eligible patients with native papilla undergoing ERCP were randomly assigned in a 1:1 ratio (with a computer-generated list) to universal pre-procedural indometacin or post-procedural indometacin in only high-risk patients, with stratification by trial centres and block size of ten. In the universal indometacin group, all patients received a single dose (100 mg) of rectal indometacin within 30 min before ERCP. In the risk-stratified, post-procedural indometacin group, only patients at predicted high risk received rectal indometacin, immediately after ERCP. Investigators, but not patients, were masked to group allocation. The primary outcome was overall ocurrence of post-ERCP pancreatitis. The analysis followed the intention-to-treat principle. This study was registered with ClinicalTrials.gov, number NCT02002650.

Findings Between Dec 15, 2013, and Sept 21, 2015, 2600 patients were randomly assigned to universal, pre-procedural indometacin (n=1297) or risk-stratified, post-procedural indometacin (n=1303). Overall, post-ERCP pancreatitis occurred in 47 (4%) of 1297 patients assigned to universal indometacin and 100 (8%) of 1303 patients assigned to risk-stratified indometacin (relative risk 0·47; 95% CI 0·34–0·66; p<0·0001). Post-ERCP pancreatitis occurred in 18 (6%) of 305 high-risk patients in the universal group and 35 (12%) of 281 high-risk patients in the risk-stratified group (p=0·0057). Post-ERCP pancreatitis was also less frequent in average-risk patients in the universal group (3% [29/992]), in which they received indometacin, than in the risk-stratified group (6% [65/1022]), in which they did not receive the drug (p=0·0003). Other than pancreatitis, adverse events occurred in 41 (3%; two severe) patients in the universal indometacin group and 48 (4%; one severe) patients in the risk-stratified group. The most common adverse events were biliary infection (22 [2%] patients *vs* 33 [3%] patients) and gastrointestinal bleeding (13 [1%] *vs* ten [1%]).

Interpretation Compared with a risk-stratified, post-procedural strategy, pre-procedural administration of rectal indometacin in unselected patients reduced the overall occurrence of post-ERCP pancreatitis without increasing risk of bleeding. Our results favour the routine use of rectal indometacin in patients without contraindications before ERCP.

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Introduction

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). The frequency of post-ERCP pancreatitis varies between 3·8% and 13·3% in unselected prospective series.[1–4] It accounts for substantial morbidity and represents a substantial cost to health-care systems. To date, only non-steroidal anti-inflammatory drugs (NSAIDs) have been shown as effective in the prevention of post-ERCP pancreatitis.[5,6]

NSAIDs have been used to prevent post-ERCP pancreatitis in high-risk patients[7,8] and in unselected patients,[6,9] and use of NSAID prophylaxis in high-risk patients minimises potential bleeding complications. However, a substantial risk of post-ERCP pancreatitis could be incurred by average-risk patients undergoing ERCP.[10,11] On the basis of findings from several meta-analyses, the European Society of Gastrointestinal Endoscopy and Japanese Society of Hepato-Biliary-Pancreatic Surgery guidelines recommended routine

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Research in context

Evidence before this study

Post-procedural pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), and incurs lengthy hospital stays and substantial financial burden. NSAIDs and pancreatic stents have been suggested for the prevention of post-ERCP pancreatitis. Rectal indometacin has been used to prevent post-ERCP pancreatitis in patients at high or average risk for the complication. However, it remains unclear as to the optimal timing of administration and the target population that would benefit most from rectal indometacin. We searched PubMed, Embase, Web of Science, and the Cochrane Library for clinical trials published in English between Jan 1, 1980, and March 1, 2016, with the terms ("pancreatitis", "post-ERCP pancreatitis", "PEP", "ERCP", or "complication") and ("NSAIDs", "indometacin", "indomethacin", or "indocin"). Before Dec 15, 2013 (when this study started), four randomised controlled trials had been published, including 1470 patients. A meta-analysis suggested that rectal indometacin reduced the occurrence of overall post-ERCP pancreatitis by 47% in patients undergoing ERCP. Subgroup analysis showed that indometacin could decrease the frequency of post-ERCP pancreatitis whether administered before or after the procedure. The beneficial effect was confirmed in both average-risk and high-risk patients. One dose of rectal indometacin did not increase the risk of post-ERCP bleeding. These findings formed the basis for this study in comparing the two different strategies of indometacin dosing to prevent post-ERCP pancreatitis. During the conduct of this study, another four randomised controlled trials were published. Findings from a meta-analysis including all eight trials (a total of 3289 patients) suggested that rectal indometacin reduced the occurrence of overall post-ERCP pancreatitis by 37% in patients undergoing ERCP.

Added value of this study

In this multicentre, randomised controlled trial, the strategy of pre-procedural administration of rectal indometacin in unselected patients further reduced the risk of post-ERCP pancreatitis by 53% (from 8% [100 patients] to 4% [47 patients]; relative risk 0·47, 95% CI 0·34–0·66), as compared with the strategy of post-procedural use in only high-risk patients. In average-risk patients, the administration of indometacin before ERCP decreased the occurrence of post-ERCP pancreatitis by 55% (from 6% [65 patients] to 3% [29 patients]; relative risk 0·46, 95% CI 0·30–0·71). In high-risk patients, rectal indometacin was best given before ERCP instead of after ERCP. Our findings also showed that a single dose of rectal indometacin did not increase other complications in patients undergoing ERCP.

Implications of all the available evidence

Because of the potential harm and unpredictable occurrence of post-ERCP pancreatitis, there is a need for an effective prophylaxis. Compared with pancreatic stenting, rectal indometacin is a more convenient and inexpensive method to prevent this complication. Consistent with the recently published guidelines of the European Society of Gastrointestinal Endoscopy and Japanese Society of Hepato-Biliary-Pancreatic Surgery for prevention of post-ERCP pancreatitis, we suggest that routine rectal administration of indometacin be considered before ERCP in all patients without contraindication.

rectal administration of the NSAID indometacin in unselected (both high-risk and average-risk) patients to prevent post-ERCP pancreatitis.[12,13] It remains unclear whether the prophylactic use of rectal NSAIDs in unselected patients is a better strategy than administration only in high-risk patients.

The serum concentrations of indometacin given as rectal suppository peak at 30–90 min after administration.[14] The effectiveness of indometacin in inhibiting the inflammatory cascade of pancreatitis is affected by the timing of administration. Findings from three meta-analyses showed that pre-ERCP administration of indometacin was more effective in reducing the frequency of post-ERCP pancreatitis[15–17] compared with post-ERCP use. Furthermore, three trials[14,18,19] have explored the use of pre-procedural indometacin in unselected patients, suggesting a potential reduction in post-ERCP pancreatitis of 24–67% compared with the use of placebo[14,18] or glycerin.[19] However, there was no direct comparison of pre-ERCP and post-ERCP administration of indometacin.

Further studies are necessary to evaluate the potential benefits and risks of indometacin in selected populations and to determine the optimal timing of indometacin administration to prevent post-ERCP pancreatitis.[20,21] We hypothesised that, compared with post-procedural use in high-risk patients, pre-procedural administration of indometacin in unselected patients might be a better strategy to prevent post-ERCP pancreatitis. This approach, achieving an optimal peak serum concentration, could also be beneficial for the average-risk patients to prevent possible pancreatic inflammation. In a prospective, multicentre, randomised controlled trial, we aimed to establish whether the prophylactic administration of rectal indometacin in unselected patients before ERCP was superior to post-procedural use in only high-risk patients to prevent post-ERCP pancreatitis.

Methods

Study design and participants

This prospective, randomised controlled trial was done in six tertiary referral hospitals in China. Patients (aged 18–90 years) with native papilla planned for diagnostic or therapeutic ERCP were eligible for enrolment in the study. Exclusion criteria included contraindications to ERCP, known pancreatic head mass, previous biliary

sphincterotomy without planned contrast injection into the pancreatic duct, allergy to NSAIDs, receiving NSAIDs within 7 days, contraindication to NSAIDs (including gastrointestinal haemorrhage within 4 weeks or renal dysfunction with serum creatinine >120 μmol/L), presence of coagulopathy or received anticoagulation therapy within 3 days, acute pancreatitis within 3 days, ERCP for biliary stent removal or exchange without anticipated pancreatogram, known active cardiovascular or cerebrovascular disease, unwilling or inability to provide consent, and pregnant or breastfeeding women. Indications or contraindications for ERCP were determined by endoscopists or anaesthesiologists before ERCP; these included risks to patient health or life judged to outweigh the potential benefit of ERCP, known or suspected perforated viscus, and haemodynamic instability (appendix).

The risk stratification of the patients was defined based on criteria used in the study by Elmunzer and colleages.[8] Patients were considered high risk for post-ERCP pancreatitis if they met at least one of the major criteria or two or more of the minor criteria (appendix). The risk status of the patients was determined immediately after the procedure by one investigator at each site who was masked to group allocation.

The trial protocol was approved by the ethics committee of each hospital. All of the patients or their legal representatives provided written informed consent. The study was done in accordance to the Helsinki Declaration and Good Clinical Practice.

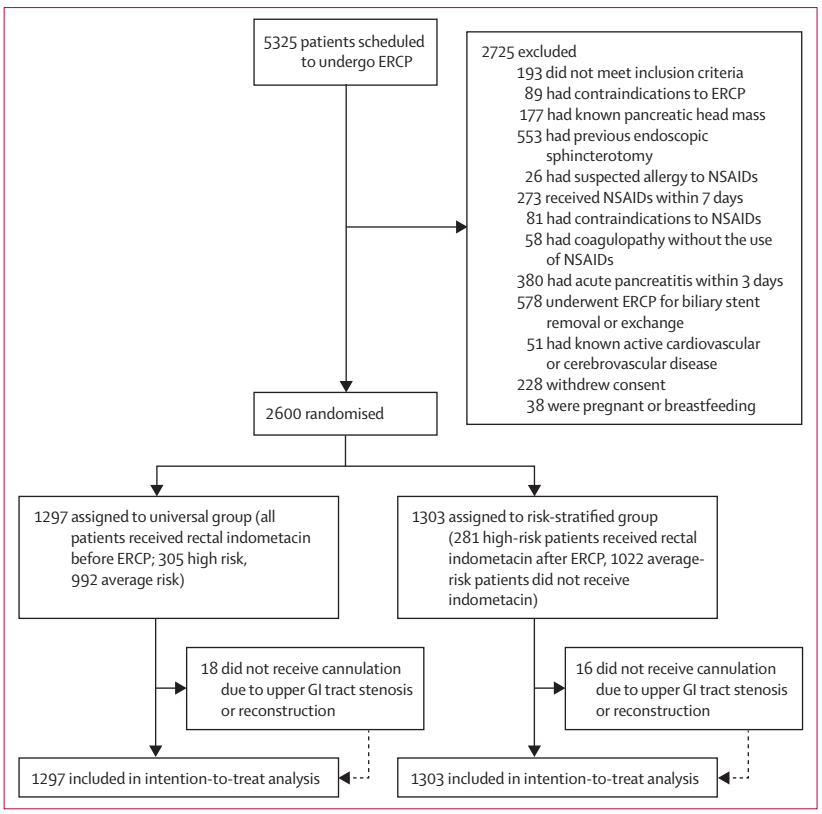

Figure 1: **Trial profile**
Contraindications to NSAIDs included gastrointestinal haemorrhage within the past 4 weeks or renal dysfunction with serum creatinine >120 μmol/L. ERCP=endoscopic retrograde cholangiopancreatography. NSAID=non-steroidal anti-inflammatory drug. GI=gastrointestinal.

Randomisation and masking

The study coordinator did the block randomisation (ten in each block). The randomisation list was computer generated, and stratified according to individual centres. Patients were assigned randomly in a 1:1 ratio (1–7 h before ERCP, usually on the morning of the procedure), before receiving ERCP, to either the universal pre-procedural group or the risk-stratified post-procedural group. Rectal indometacin was administered in the procedure room before or after ERCP by one investigator in each site who did not participate in data collection and analysis. These investigators and patients were instructed not to disclose if or when rectal indometacin was used. Endoscopists and assistances who participated in ERCP procedures were masked to group allocation. Investigators who collected demographic or procedure-related data or participated in the assessment of post-ERCP complications were also masked to group allocation. Patients were not masked to treatment allocation.

Before the start of this study, post-procedural selective indometacin in high-risk patients had been demonstrated as effective in the prevention of post-ERCP pancreatitis.[8] However, no studies had been reported then to evaluate the effect of post-procedural indometacin in average-risk patients. To prevent potential risk of bleeding and other adverse events in average-risk patients, we set post-procedural selective indometacin in high-risk patients as the control group in this study.

See Online for appendix

Procedures

All patients assigned to the universal group received a single dose of rectal indometacin 100 mg (Sinopharm Wuhan ZhongLian SiYao Pharmaceutical Co, China) within 30 min before ERCP. In the risk-stratified group, only high-risk patients received rectal indometacin 100 mg immediately after ERCP, whereas average-risk patients did not receive indometacin.

ERCP was performed as described previously.[22] Briefly, all patients initially received wire-guided cannulation with a sphincterotome (Dreamtome, Boston Scientific, Natick, MA, USA). If cannulation failed, precut sphincterotomy or the double-wire technique was performed when appropriate. Therapeutic manipulation (eg, sphincterotomy, balloon dilation, stone extraction, and stenting) was done when appropriate. Pancreatic duct stent placement was performed at the discretion of the endoscopists.

Outcomes

The primary outcome of the study was the frequency of post-ERCP pancreatitis. The diagnosis of post-ERCP pancreatitis was established if there was new onset of

upper abdominal pain associated with an elevated serum amylase of at least three times the upper limit of normal range at 24 h after the procedure, and admission to hospital for at least 2 nights. The secondary outcome was the frequency of moderate to severe post-ERCP pancreatitis. We defined severity of pancreatitis according to the criteria reported by Cotton and colleagues (appendix).[23]

Other post-ERCP complications (including bleeding, biliary infection, perforation, and any adverse outcomes requiring hospital admission or prolonged hospital stay for further management) were monitored as described previously.[24] Moderate to severe bleeding was defined as clinically significant bleeding with decrease in haemoglobin concentration of at least 3 g/L with the need for transfusion, angiographic intervention, or surgery. [23] Patients were contacted at 30 days to assess late complications (including delayed bleeding or cardiovascular or renal adverse events); this was the final follow-up.

	Pre-procedural indometacin in all patients (n=1297)	Post-procedural indometacin in high-risk patients* (n=1303)
Age, years	62 (50–72)	63 (50–74)
Sex		
Men	618 (48%)	619 (48%)
Women	679 (52%)	684 (52%)
Body-mass index, kg/m²	22·6 (20·5–24·9)	22·6 (20·4–24·8)
Coexisting disorders		
Hypertension	263 (20%)	271 (21%)
Diabetes	127 (10%)	133 (10%)
Coronary heart disease	96 (7%)	101 (8%)
Chronic pulmonary disease	38 (3%)	38 (3%)
Liver cirrhosis	23 (2%)	20 (2%)
Indications		
CBDS	1013 (78%)	1002 (77%)
Malignant biliary stricture	146 (11%)	170 (13%)
Benign or undetermined biliary stricture	92 (7%)	87 (7%)
Suspected sphincter of Oddi dysfunction	35 (3%)	45 (3%)
Benign pancreatic diseases	34 (3%)	37 (3%)
Others	31 (2%)	30 (2%)
Previous history of ERCP	13 (1%)	12 (1%)
Previous history of post-ERCP pancreatitis	3 (<1%)	1 (<1%)
Cholecystectomy	478 (37%)	485 (37%)
Surgically altered gastrointestinal tract		
Billroth I	4 (<1%)	6 (<1%)
Billroth II	12 (1%)	13 (1%)
Roux-en-Y	1 (<1%)	1 (<1%)

Data are n (%) or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. CBDS=common bile duct stone. *The definition of high-risk patients is described in the appendix.

Table 1: **Baseline characteristics**

An investigator who was familiar with ERCP at each site and masked to treatment allocation recorded the procedure-related parameters including cannulation methods, numbers of cannulation attempts, and inadvertent pancreatic duct cannulation, pancreatography, and prophylactic placement of pancreatic duct stent. The same investigator also recorded the patient demographics, post-ERCP adverse events potentially caused by the procedure or study drug, and follow-up data. All data were subsequently entered into a web-based database and managed by independent investigators.

We defined severity of post-ERCP complications according to the Cotton criteria:[23] mild (pancreatitis after the procedure requiring admission or prolongation of planned admission to 2–3 days); moderate (pancreatitis after the procedure requiring hospitalisation of 4–10 days); and severe (pancreatitis after the procedure requiring hospitalisation for more than 10 days, or haemorrhagic pancreatitis, phlegmon or pseudocyst, or intervention). Detailed definitions for other adverse events are provided in the appendix.

Statistical analysis

Before the initiation of the study, a biostatistician and one of the principle investigators (YP) worked together to determine the power calculation for this study. We assumed a frequency of post-ERCP pancreatitis in the risk-stratified indometacin group of about 5·0%, based on previous studies.[2,3] Based on relative risk reductions of 24–67% in previous studies of pre-procedural indometacin in unselected patients,[14,18,19] we assumed a relative risk reduction of 50% in the universal indometacin group with a frequency of post-ERCP pancreatitis of 2·5%. Considering a possible withdrawal rate of 6% (for example, due to failure to reach papilla because of duodenal stenosis, altered anatomy, or unexpected situation), about 1300 patients in each group were required to detect a difference between the two study arms, with a power of 90% and a two-sided significance level of 0·05.

We analysed data in the intention-to-treat population, including all patients who underwent randomisation (irrespective of whether they successfully received cannulation). We compared the baseline characteristics of the patients in the two study groups. We expressed quantitative variables as medians and IQRs and used the Mann-Whitney *U* test to compare the results. We used χ^2 tests or Fisher's exact test to compare the qualitative variables, as appropriate. We compared the occurrence of the primary and secondary endpoints between the two groups. Results are presented as relative risk (RR) with 95% CIs. Additionally, we tested the treatment-by-subgroup interaction effect to assess whether the treatment effect differed in the following prespecified subgroups: age, sex, high-risk patients, suspected sphincter of Oddi dysfunction (defined

	Pre-procedural indometacin in all patients (n=1297)	Post-procedural indometacin in high-risk patients* (n=1303)
ERCP type		
Diagnostic	50 (4%)	47 (4%)
Therapeutic	1247 (96%)	1256 (96%)
Targeted duct		
Common bile duct	1257 (97%)	1261 (97%)
Pancreatic duct	40 (3%)	42 (3%)
Success rate of cannulation	1257 (97%)	1260 (97%)
Failed cannulation		
Papilla not found	18 (1%)	16 (1%)
Technical difficulty	22 (2%)	27 (2%)
Cannulation method†		
Standard	1071 (83%)	1107 (85%)
Double wire	35 (3%)	30 (2%)
Precut	173 (13%)	150 (12%)
Cannulation attempts, median (range)*†	3 (1–5)	2 (1–5)
Inadvertent pancreatic duct cannulation, median (range)†	0 (0–1)	0 (0–1)
High-risk patients*	305 (24%)	281 (22%)
Clinical suspicion of sphincter of Oddi dysfunction	35 (3%)	45 (3%)
History of post-ERCP pancreatitis	3 (<1%)	1 (<1%)
Precut sphincterotomy	173 (13%)	150 (12%)
Pancreatic sphincterotomy	96 (7%)	81 (6%)
Difficult cannulation (≥8 attempts)	196 (15%)	169 (13%)
Balloon dilatation of an intact biliary sphincter	1 (<1%)	5 (<1%)
Women younger than 50 years	169 (13%)	178 (14%)
History of recurrent pancreatitis (≥2 times)	23 (2%)	35 (3%)
Pancreatography ≥3 times and ≥1 injection to the tail of pancreas	0	3 (<1%)
Ampullectomy	5 (<1%)	1 (<1%)
Trainee involvement	302 (23%)	294 (23%)
Prophylactic pancreatic duct stent	63 (5%)	57 (4%)

Data are n (%) or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. *The definition of high-risk patients is described in the appendix. †Calculated in patients with attempted cannulation.

Table 2: **Procedure-related parameters and high-risk factors for post-ERCP pancreatitis**

	Pre-procedural indometacin in all patients (n=1297)	Post-procedural indometacin in high-risk patients* (n=1303)	Relative risk (95% CI)	p value
Post-ERCP pancreatitis	47 (4%)	100 (8%)	0·47 (0·34–0·66)	<0·0001
Mild	36 (3%)	77 (6%)	0·47 (0·32–0·69)	<0·0001
Moderate to severe	11 (1%)	23 (2%)	0·48 (0·24–0·98)	0·040
Post-ERCP pancreatitis in high-risk patients*	18/305 (6%)	35/281 (12%)	0·47 (0·27–0·82)	0·0057
Mild	14 (5%)	29 (10%)	0·45 (0·24–0·82)	0·0079
Moderate to severe	4 (1%)	6 (2%)	0·61 (0·18–2·15)	0·44
Post-ERCP pancreatitis in average-risk patients	29/992 (3%)	65/1022 (6%)	0·46 (0·30–0·71)	0·0003
Mild	22 (2%)	48 (4%)	0·47 (0·29–0·78)	0·0024
Moderate to severe	7 (1%)	17 (2%)	0·42 (0·18–1·02)	0·048
Gastrointestinal bleeding	13 (1%)	10 (1%)	1·31 (0·57–2·97)	0·52
Mild	5 (<1%)	4 (<1%)	1·26 (0·34–4·67)	0·75
Moderate	6 (<1%)	5 (<1%)	1·21 (0·37–3·94)	0·78
Severe	2 (<1%)	1 (<1%)	2·01 (0·18–22·13)	0·62
Biliary infection	22 (2%)	33 (3%)	0·67 (0·39–1·14)	0·14
Mild	15 (1%)	24 (2%)	0·63 (0·33–1·19)	0·15
Moderate	7 (1%)	9 (1%)	0·78 (0·29–2·09)	0·62
Severe	0	0	..	..
Perforation	1 (<1%)	0	..	..
Other adverse events	5 (<1%)	5 (<1%)	..	..
Pulmonary infection	2 (<1%)	5 (<1%)	0·40 (0·08–2·07)	0·45
Incomplete bowel obstruction	3 (<1%)	0	..	..
Length of post-ERCP hospital stay (days)	2 (1–4)	3 (1–4)	..	0·17

Data are n (%), n/N (%), or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. *The definition of high-risk patients is described in the appendix.

Table 3: **Outcomes and adverse events**

in appendix), precut sphincterotomy, pancreatic sphincterotomy, difficult cannulation, women younger than 50 years, history of recurrent pancreatitis, pancreatography, placement of a pancreatic duct stent, trainee involvement, targeted duct, and cannulation methods.

No interim analysis was done. All tests were two-sided, and a p value of less than 0·05 was considered statistically significant. Analyses were done with Stata (version 12.0) statistical software. This trial is registered with ClinicalTrial.gov, number NCT02002650.

Role of the funding source

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Results

From Dec 15, 2013, to Sept 21, 2015, 5325 consecutive patients who were scheduled to undergo ERCP in six centres were considered for the study. After screening, 2725 patients were excluded (193 patients did not meet inclusion criteria, 2304 met exclusion criteria, and 228 declined to participate; figure 1). The remaining 2600 patients were randomly assigned to the universal indometacin group (n=1297) or the risk-stratified indometacin group (n=1303). ERCP was not done in

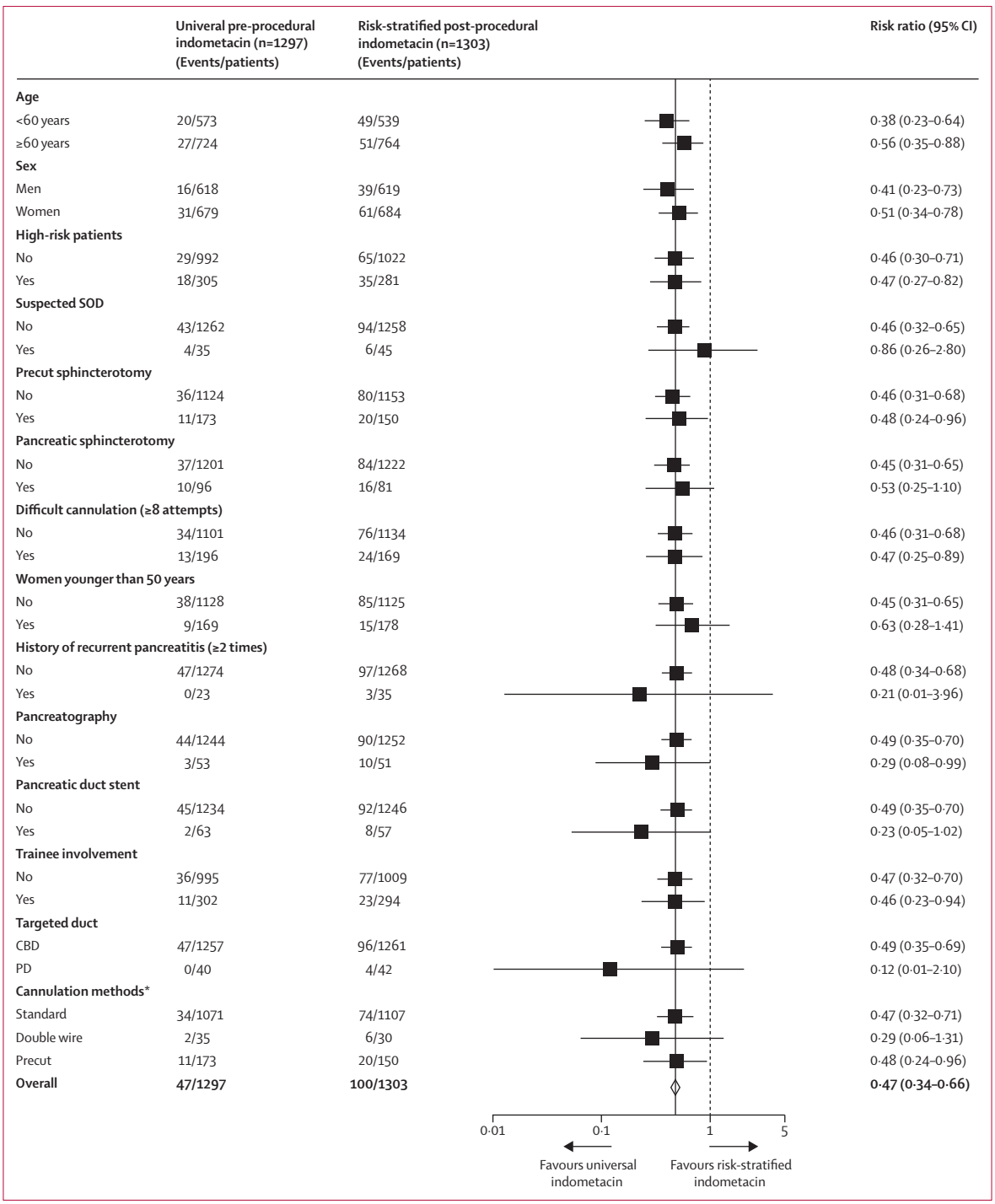

Figure 2: **Subgroup analyses**
The reduction in the risk of post-ERCP pancreatitis with a universal strategy, as compared with a risk-stratified strategy, was consistent across major subgroups. There were no significant interactions in any of the predefined subgroups (p>0·10 for all comparisons). ERCP=endoscopic retrograde cholangiopancreatography. SOD=sphincter of Oddi dysfunction. *Data about cannulation method were unavailable for 34 patients without cannulation.

34 (1%) patients because the papilla could not be reached, due to a finding of secondary to upper gastrointestinal-tract stenosis, or because of previous surgical reconstruction (figure 1). Baseline characteristics of the two groups are shown in table 1. The median age was 62 years (IQR 50–73), and more than half of the patients

were women. As shown in table 2, ERCP procedure-related parameters and the proportion of patients at high risk for post-ERCP pancreatitis in the two groups were similar. Successful cannulation was achieved in 2517 (97%) patients, and trainees were involved in 596 (23%) of the procedures. 586 (23%) patients were at high risk of post-ERCP pancreatitis. The two most common risk factors included precut sphincterotomy (323 [12%] patients) and difficult cannulation with eight or more cannulation attempts (365 [14%] patients). Most (105 [88%]) of the 120 patients who received prophylactic pancreatic stenting were at high risk of post-ERCP pancreatitis.

Overall, post-ERCP pancreatitis occurred in 47 (4%) patients who received universal pre-procedural indometacin, compared with 100 (8%) patients in the risk-stratified post-procedural indometacin group (difference 4·1%, 95% CI 2·3–5·8; relative risk [RR] 0·47, 95% CI 0·34–0·66; p<0·0001; table 3). Compared with the risk-stratified group, the universal group had significant reduction in the frequency of mild and moderate-to-severe post-ERCP pancreatitis (table 3). The frequency of post-ERCP pancreatitis in high-risk patients was 6% (18/305) in the universal group and 12% (35/281) in the risk-stratified group (table 3). Post-ERCP pancreatitis in occurred in 29 (3%) of 992 average-risk patients in the universal indometacin group compared with 65 (6%) of 1022 average-risk patients in the risk-stratified indometacin group (table 3).

Clinically significant gastrointestinal bleeding did not significantly differ between the two groups (13 [1%] patients in the universal group *vs* ten [1%] in the risk-stratified group; table 3). Moderate-to-severe bleeding was reported in eight (1%) patients assigned to universal pre-procedural indometacin and six (<1%) patients assigned to risk-stratified post-procedural indometacin (table 3). Biliary infection was reported in 22 (2%) patients in the universal group and 33 (3%) patients in the risk-stratified group (table 3). There was one (<1%) patient with mild perforation in the universal group, caused by precut papillotomy which resolved spontaneously with conservative treatment. The patient was discharged home 3 days later. There were no significant differences between the two groups regarding pulmonary infection and incomplete bowel obstruction (table 3). There were no cardiovascular or renal adverse events and no deaths reported in this study. The median length of post-ERCP hospital stay was 2 days (IQR 1–4) in the universal indometacin group and 3 days (IQR 1–4) in the risk-stratified indometacin group (p=0·17).

The beneficial effect consistently favoured the universal pre-procedural indometacin across most of the prespecified subgroups (figure 2). There were no significant interactions in any of the predefined subgroups (p>0·10 for all comparisons).

Discussion

Although rectal indometacin has been widely used for the prevention of post-ERCP pancreatitis in the past 3 years, the target population and optimal time of administration have not been well defined. In this multicentre, randomised controlled trial, we found that pre-procedural administration of rectal indometacin in unselected patients further reduced the risk of post-ERCP pancreatitis by 53% compared with the post-procedural use of indometacin in only high-risk patients. The universal strategy was associated with an absolute risk reduction of 4·1% (95% CI 2·3–5·8), equivalent to treating 25 unselected patients to prevent one case of post-ERCP pancreatitis. Additionally, the pre-ERCP strategy did not increase the frequency of clinically significant gastrointestinal bleeding or other complications. This large-scale study provides direct evidence to support the recommendation that routine rectal administration of NSAIDs should be given in all patients without contraindications, published in the European Society of Gastrointestinal Endoscopy and Japanese Society of Hepato-Biliary-Pancreatic Surgery guidelines to prevent post-ERCP pancreatitis.[12,13] Furthermore, our study findings suggest that rectal indometacin should be administrated before ERCP instead of after ERCP.

The overall frequency of post-ERCP pancreatitis in our study was 6% (147 of 2600 patients), which seems higher than that reported in other studies.[25,26] This might result from the exclusion of patients with a previous history of endoscopic sphincterotomy or suspected pancreatic cancer, in whom post-ERCP pancreatitis is very uncommon.[27,28] The frequency of post-ERCP pancreatitis among unselected patients in the universal indometacin group in our study was 4% (47 of 1297 patients), which was similar to the 3·2–8·5% reported in five other randomised controlled trials using the same pre-procedural universal strategy.[14,18,19,29,30] Post-ERCP pancreatitis among high-risk patients who received rectal indometacin immediately after ERCP (12%; 35/281) seemed more common in our study than previously reported by Elmunzer and colleagues[8] (9%; 27/295). The high-risk patients in our trial were older than those in Elmunzer and colleagues' study (mean age 61 years [SD 15] *vs* 45 years [SD 13]) and there were more men (41% [243/586] *vs* 21% [126/602]), with less clinical suspicion of sphincter of Oddi dysfunction (14% [80/586] *vs* 82% [495/602]), and less therapeutic pancreatic sphincterotomy (30% [177/586] *vs* 57% [342/602]). The differences in high-risk characteristics of the patients between the two studies might account for the difference in post-ERCP pancreatitis.

Prophylactic pancreatic duct stenting is useful to reduce the liklihood of post-ERCP pancreatitis in high-risk patients.[12,13] However, it remains unclear whether pancreatic duct stent alone is more effective than indometacin. Two clinical trials comparing the efficacies of pancreatic duct stenting and indometacin are ongoing (ClinicalTrials.gov NCT02476279 and NCT02368795). In

a network meta-analysis,[31] the combination of pancreatic duct stenting and NSAIDs did not further reduce the risk of post-ERCP pancreatitis compared with the use of NSAIDs alone. Placement of a pancreatic duct stent can be technically challenging in some difficult cases, and an unsuccessful attempt has been reported to increase the risk of post-ERCP pancreatitis.[32] Because the evidence is not conclusive regarding the role of pancreatic duct stenting in high-risk patients receiving rectal indometacin, the use of such a stent was at the discretion of the endoscopists in our study. Only 18% (105/586) of high-risk patients received a pancreatic duct stent in our study, which was substantially lower than the 82% (496/602) reported by Elmunzer and colleagues.[8]

Findings from two randomised controlled trials[7,8] have shown benefit of rectal indometacin in high-risk patients for reducing post-ERCP pancreatitis.[7,8] The effects of indometacin in unselected patients had been investigated in five randomised controlled trials.[14,18,19,29,30] However, only one study[30] included data about post-ERCP pancreatitis in average-risk patients. Although no significant difference of post-ERCP pancreatitis was noted between use versus no use of indometacin in average-risk patients, the study reported by Patai and colleagues[30] lacked statistical power to assess this comparison due to the small number of average-risk patients included (n=99). In our study, three-quarters of the enrolled patients were of average risk, and the results showed that post-ERCP pancreatitis occurred even in average-risk patients at a frequency of 6% (65/1022), consistent with previous reported studies.[33,34] Additionally, rectal indometacin reduced the relative risk of post-ERCP pancreatitis by 55% (from 6% to 3%) among average-risk patients. Because the predictive accuracy of post-ERCP pancreatitis based on risk factors associated with patient characteristics and ERCP procedure is not satisfactory, we propose that rectal indometacin should be routinely administered even in average-risk patients.

The time of administration of rectal indometacin has varied among different studies, from before ERCP or during the procedure to after ERCP (appendix). Our data showed that administration of indometacin before ERCP could further reduce the frequency of post-ERCP pancreatitis from 12% (35/281) to 6% (18/305) in high-risk patients, a finding that is consistent with the results of several meta-analyses.[15–17] Early administration of indometacin might achieve better efficacy because of the more appropriate peak serum concentration attained to prevent pancreatic inflammation. In a recent study of 449 patients,[35] rectal indometacin administrated during ERCP did not prevent post-ERCP pancreatitis (appendix). However, more than 30% of patients enrolled in this study had previous sphincterotomy and nearly 18% of patients underwent concomitant endoscopic ultrasound/fine needle aspiration, which is a departure from other randomised controlled trials.[7,8,14,18,19,29,30]

Antiplatelet or anticoagulant drugs (eg, aspirin and clopidogrel) have been recommended to be discontinued before endoscopic sphincterotomy in some patients at high risk of bleeding.[36,37] To avoid possible interferences with the outcomes of this study, we excluded patients who received NSAIDs within 7 days before ERCP. Findings from four randomised controlled trials, as well as the current study, suggest that one-dose administration of rectal indometacin before or after ERCP does not increase the risk of bleeding.[7,8,14,27] The frequency of clinically significant bleeding was 1% (23 of 2600 patients) in our trial, which was similar to that reported in previous studies;[3,11,26,38,39] we did not note significant differences between the treatment groups. However, our study was not powered to compare the rates of bleeding. A larger study sample or data from large population-based databases or registries will be helpful to better characterise the risk of bleeding in patients receiving rectal indometacin.

The strengths of our study include its multicentre randomised design and large sample size. Moreover, in subgroup analyses, the relative treatment effect of the pre-ERCP strategy was consistent across a wide variety of important, prespecified subgroups, supporting the generalisability of the results.

There are some limitations to our study. First, because of the difference in timing of indometacin administration in the two groups, the patients could not be masked to treatment assignment. However, objective and measurable outcomes (eg, amylase concentration and length of hospital stay) were evaluated after the procedure by investigators masked to treatment assignment, reducing the possibility of bias. Second, patients with previous endoscopic biliary sphincterectomy were excluded from this study. Although post-ERCP pancreatitis rarely occurs in this group of patients, it remains unclear whether they would benefit from rectal indometacin.[27] Third, we calculated the frequency of pulmonary infection and incomplete bowel obstruction on the basis of very small numbers. The lack of a significant difference between the two groups might result from type II error, and needs to be further investigated. This study was also done in tertiary hospitals in China, and the findings need to be validated in different clinical settings.

In conclusion, the strategy of prophylactic pre-ERCP administration of rectal indometacin in all patients is superior to the strategy of purposeful rectal indometacin given after ERCP in only high-risk patients to reduce the risk of post-ERCP pancreatitis. The single-dose administration of rectal indometacin before ERCP did not increase the risk of post-ERCP bleeding.

Contributors

YP and XGG conceived and designed the study. RZ, ZL, XW, BW, ZN, TL, XL, WZ, LZhang, QW, ML, YZ, QL, HS, ZW, and QT acquired the data. LZhao and JL analysed and interpreted the data. HL and YP drafted and edited the manuscript. JL, XGG, and SL critically reviewed the manuscript for important intellectual content. HL, LZhao, and XYG did the statistical analysis. KW and DF provided administrative and material support. The authors alone are responsible for the content and the writing of the paper.

Declaration of interests

We declare no competing interests.

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