**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 8929**

**Columns: RANDOMIZED CONTROLLED TRIAL**

**Is rectal indomethacin effective in preventing of post-endoscopic retrograde cholangiopancreatography pancreatitis?**

Döbrönte Z *et al* Indomethacin and post-ERCP pancreatitis

Zoltán Döbrönte, Zoltán Szepes, Ferenc Izbéki, Judit Gervain, László Lakatos, Gyula Pécsi, Miklós Ihász, Lilla Lakner, Erzsébet Toldy, László Czakó

**Zoltán Döbrönte, Miklós Ihász, Lilla Lakner,** Department of Gastroenterology and Internal Medicine, Markusovszky Teaching Hospital, H-9700 Szombathely, Hungary

**Zoltán Szepes, László Czakó,** 1st Department of Internal Medicine, University of Szeged, H-6722 Szeged, Hungary

**Ferenc Izbéki, Judit Gervain,** 1st Department of Internal Medicine, Szent György Regional Hospital, H-8000 Székesfehérvár, Hungary

**László Lakatos,** Department of Internal Medicine, Csolnoky Ferenc Regional Hospital, H-8200 Veszprém, Hungary

**Gyula Pécsi,** Department of Gastroenterology, Karolina Hospital, H-9200 Mosonmagyaróvár, Hungary

**Erzsébet Toldy,** Central Laboratory, Markusovszky Teaching Hospital, H-9700 Szombathely, Hungary

**Erzsébet Toldy,** Institute of Diagnostics, Faculty of Health Sciences, University of Pécs, H-7621 Pécs, Hungary

**Author contributions:** Döbrönte Z and Czakó L designed the research; Döbrönte Z, Szepes Z, CzakóL, Izbéki F, Gervain J, Lakatos L, Ihász M, Lakner L and Pécsi G performed the research; Toldy E analysed the data; Döbrönte Z wrote the paper.

**Supported by** TÁMOP-4.2.2.A-11/1/KONV-2012-0035 and OTKA K101521

**Correspondence to: László Czakó, MD, PhD,** First Department of Medicine, University of Szeged, Dugonics tér, H-6701 Szeged, Hungary. czako.laszlo@med.uszeged.hu

**Telephone:** +36-62-545187 **Fax:** +36-62-545185

**Received:** January 12, 2014 **Revised:** March 12, 2014

**Accepted:** April 21, 2014

**Published online:**

**Abstract**

**AIM:**To investigate the effectiveness of rectally administered indomethacin in the prophylaxis of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and hyperamylasaemia in a multicentre study.

**METHODS:** A prospective randomised placebo-controlled multicentre study in 5 endoscopic units was conducted on 686 patients randomised to receive a suppository containing 100 mg indomethacin or an inert placebo 10-15 min before ERCP. Post-ERCP pancreatitis and hyperamylasaemia were evaluated 24 h following the procedure on the basis of clinical signs and laboratory parameters and computed tomography/magnetic resonance imaging findings if required.

**RESULTS:** Twenty-one patients were excluded due to the incompleteness of their data or because of protocol violation. The results of 665 investigations were evaluated: 347 in the indomethacin group and 318 in the placebo group. The distributions of the risk factors in the two groups did not differ significantly. Pancreatitis developed in 42 patients (6.3%), it was mild in 34 (5.1%) and severe in 8 (1.2%) cases. Hyperamylaesemia occurred in 160 patients (24.1%). There was no significant difference between the indomethacin and placebo groups in the incidence of either post-ERCP pancreatitis (5.8% *vs* 6.9%) or hyperamylasaemia (23.3% *vs* 24.8%). Similarly, subgroup analysis did not reveal any significant differences between the two groups.

**CONCLUSION:**100 mg rectal indomethacin administered before ERCP did not proved effective in preventing post-ERCP pancreatitis.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Hyperamylasaemia; Non-steroidal anti-inflammatory drugs; Indomethacin

**Core tip:** Acute pancreatitis is the most common and potentially fatal complication of endoscopic retrograde cholangiopancreatography (ERCP). Non-steroidal anti-inflammatory drugs have been suggested to be effective in prospective controlled trials, but the results are inconclusive. A prospective randomised placebo-controlled multicentre study was therefore conducted in 5 endoscopic units. The results on a total of 665 patients who randomly received a suppository containing 100 mg indomethacin or placebo before ERCP were evaluated. There was no difference between the indomethacin and placebo groups in the incidence of either post-ERCP pancreatitis or hyperamylasaemia. Rectal indomethacin is not effective in preventing post-ERCP pancreatitis in average-risk patients.

Döbrönte Z, Szepes Z, Izbéki F, Gervain J, Lakatos L, Pécsi G, Ihász M, Lakner L, Toldy E, Czakó L. Is rectal indomethacin effective in preventing of post-endoscopic retrograde cholangiopancreatography pancreatitis?

*World J Gastroenterol* 2014; In press

**Available from:** URL: http://www.wjgnet.com/esps/

**DOI:** <http://dx.doi.org/10.3748/wjg.v20.i0.0000>

**INTRODUCTION**

Among the gastrointestinal endoscopic procedures, endoscopic retrograde cholangiopancreatography (ERCP) has the greatest potential for complications. The most common complication is acute pancreatitis, with a reported overall incidence of 2-10%, but this can rise to even 30% in the presence of certain risk factors. Post-ERCP pancreatitis is most often mild, but in around 10% of the cases (0.4%-0.6% of the procedures performed) it is severe and potentially fatal. The mortality rate is about 0.1-0.5%. Furthermore, asymptomatic hyperamylasaemia occurs in 35%-70% of patients undergoing ERCP. The wide interval of the published incidence of pancreatitis can be explained by the different criteria used for the diagnosis, the type and the duration of the follow-up of the patients involved in the studies, the level of endoscopic expertise and the frequencies of patient- and procedure-related risk factors among the investigated patient population[1,2].

 A number of agents have been tested experimentally and in clinical trials for their potential effectiveness in preventing ERCP-induced pancreatitis. Chemoprevention studies have targeted the following mechanisms of action: a reduction of pancreatic secretion, the prevention of intra-acinary trypsinogen activation, interruption of the inflammatory cascade, the relaxation of sphincter of Oddi and the prevention of infection. The majority of the investigated pharmacological agents proved to be ineffective or the results were conflicting.

 Non-steroidal anti-inflammatory drugs (NSAIDs) were recently suggested to be effective in some prospective controlled trials. NSAIDs inhibit phospholipase A2 which has an early role in the inflammatory cascade in acute pancreatitis. Inhibition of phospholipase A2 results in the suppression of several important classes of pro-inflammatory lipids (prostaglandins, leukotrieens and platelet activating factor). Indomethacin followed by diclofenac is the most potent NSAID from the aspect of phospholipase A2 inhibition. NSAIDs additionally inhibit neutrophil-endothelial cell attachment. Indomethacin has reported been decrease the mortality due to experimental pancreatitis in animals[3].

 Three meta-analyses involving the data of 4 earlier randomised controlled trials indicated that indomethacin or diclofenac rectally administering in a dose of 100 mg was effective in decreasing the incidence of post-ERCP pancreatitis[4-6]. Four recent meta-analyses likewise concluded that NSAIDs reduced the incidence and severity of post-ERCP pancreatitis[7-10]. However, the limitations of these meta-analyses are the small case numbers in of the original studies, the study heterogeneity, and the intergroup differences in the timing, type and route of NSAID administration, in theheterogeneity in the proportion of high-risk patients, and in the prophylactic placement of pancreatic stents. The benefits of multicenter trials include a larger number of participants and generalizability from conduct of the trial in several regions of the country. Other advantages are the extensive quality control and routine oversight needed to standardize procedures across centers and the contributions of multiple investigators with complementary expertise.

 In a recent study, Otsuka *et al*[11] found low-dose rectal diclofenac to be effective in the prophylaxis of post-ERCP pancreatitis, whereas in 2 other randomised controlled trials diclofenac 50 mg orally or 75 mg intramuscularly was concluded to be non-effective[12,13]. There is therefore some doubt as to the clinical effectiveness of NSAIDs in the prophylaxis of post-ERCP pancreatitis, all the more as several agents have shown promise in early single-centre studies, but the results in larger multicentre randomised controlled trials were disappointing. A survey published in 2010 on data collected from 141 endoscopists performing ERCP in 29 countries revealed that the overwhelming majority (83.7%) of the survey respondents did not use NSAIDs for post-ERCP pancreatitis prophylaxis, referring to the lack of convincing scientific evidence of its benefits[14].

 In our earlier single-centre randomised controlled trial, 100 mg indomethacin given rectally before ERCP did not prove effective in reducing the incidence of post-procedure pancreatitis[15]. In our present study, therefore, the aim was to investigate the effectiveness of rectally administered indomethacin in reducing the incidence of post-ERCP pancreatitis and hyperamylasaemia in a multicentre randomised controlled trial.

**MATERIALS AND METHODS**

***Protocol and patients***

A multicentre prospective randomised placebo-controlled trial was conducted in 5 endoscopic units (tertiary referral centres for therapeutic endoscopy) on 686 patients who consecutively underwent ERCP within inpatient care, in 2-centres between January 2012 and January 2013 and in 3 between August 2012 and January 2013. Exclusion criteria included: acute pancreatitis or hyperamylasaemia at the time of the ERCP, unsuccessful duct opacification, previous sphincterotomy, anus praeternaturalis, Billroth II surgery, a known allergy to indomethacin and the use of NSAIDs in the previous week. Placement of a pancreatic stent was not allowed. Antibiotics were permitted.

 Patients were randomly assigned to receive either a rectal suppository containing 100 mg indomethacin (Sanofi-Aventis) or an identical-appearing suppository containing the inert vechicle 10-15 min before the sedoanalgesic premedication for ERCP. The suppository administration and its retention within the rectal ampulla were supervised by an independent endoscopic nurse, who completed the list detailing the patient’s characteristics. The investigation characteristics were recorded by the investigator, who was unaware of the nature of the given suppository. The follow-up and the diagnosis according to the criteria of mild or severe pancreatitis and hyperamylasaemia were performed blindly and independently of the investigator, and the analysis was also carried out in a blinded way. The randomization was revealed only after the analysis.

 The day before and 24 h after the ERCP, the levels of serum amylase, lipase and C-reactive protein and the blood count were determined. In cases of hyperamylasaemia, the pancreatic serum enzyme levels were followed until their normalisation.

 Post-ERCP pancreatitis was diagnosed 24 h following the procedure on the basis of clinical signs and laboratory parameters, and (when required) the results of computed tomography (CT) or magnetic resonance imaging (MRI) were also taken into account. The definition of post-ERCP pancreatitis was based on consensus criteria[16]: a new onset of typical upper abdominal pain and symptoms, serum amylase and/or lipase level at least 3 times higher than the upper normal limit 24 h after the procedure, requiring a prolongation of admission, and/or CT/MRI findings consistent with the diagnosis. Severe post-ERCP pancreatitis was defined as a need for a hospital stay of more than 10 days, accompanied by a significant complication, such as pancreas necrosis, pseudocyst formation, peripancreatic fluid collection, fatty necrosis or the need for a non-surgical or surgical intervention. Hyperamylasaemia was defined as a serum amylase level above the upper normal limit 24 h after the procedure without the presence of criteria of acute pancreatitis. The definition of difficult cannulation: more than 5 cannulation attempts before successful duct opacification.

This work was carried out in full accordance with the Declaration of Helsinki (2004) of the World Medical Association. The study was approved ethically by the Regional/Local Research Ethical Committees. All patients provided their written informed consent.

***ERCP***

The indications of ERCPs were completely independent of the study investigators. The ERCPs were performed consecutively and all the patients who did not meet the exclusion criteria were included in the study. All the investigations were performed under conscious sedation with midazolam and pethidine or midazolam and fentanyl. Hioscine-*n*-butyl (Buscopan; Boeringer) was used for the controll of hyperperistalsis at the discretion of the endoscopist. For cholangiopancreatography the iodine-containing contrast material lysine amidotrizoate (Peritrast 600 mg/mL, Köhler) in 50% dilution was used. All investigations were performed under pulsoxymetry monitoring. For endoscopic sphincterotomy (EST), pure cutting current (25 W) was used.

***Statistical analysis***

Statistical significance was calculated by using *÷*2 and Fisher’s exact tests, as appropriate. Statistical analysis was performed with the Statistics for Windows 7.0 (Microsoft) program. Statistical significance was set at *P* < 0.05.

**RESULTS**

***Subject characteristics***

A total of 686 patients were randomised, of whom 14 patients were excluded from the evaluation due to the incompleteness of their data, and 7 because of a pancreatic stent placement. Accordingly, the results of 665 investigations were evaluated in total: 347 in the indomethacin group and 318 in the placebo group.

The two groups proved to be well matched from the aspects of age, sex, BMI, the duration of the procedure and the frequency of other risk factors of post-ERCP pancreatitis (Tables 1 and 2). The mean age of the patients overall was 66.62 ± 15.92 (SD) years: 65.66 ± 16.21 (SD) in the indomethacin group and 67.68 ± 15.56 (SD) in the control group.

***Post-ERCP pancreatitis***

Post-ERCP pancreatitis developed altogether in 42 (6.3%) of the 665 cases. The incidence of post-ERCP pancreatitis was not significantly different in the indomethacin and placebo groups: 5.8% (20/347) *vs* 6.9% (22/318), respectively (*P* = 0.54) (Table 3). Sixteen (4.6%) cases of mild and 4 (1.2%) of severe pancreatitis occurred in the indomethacin group, and 18 (5.7%) of mild and 4 (1.3%) of severe pancreatitis in the placebo group. Hyperamylasaemia developed in 160 (24.1%) patients overall: in 81 (23.3%) in the study group, and in 79 (24.1%) in the control group (*P* = 0.65) (Table 3).One patient died, in the placebo group, from necrotizing pancreatitis as a complication of ERCP. The subgroup analyses from the aspects of age, gender, BMI and procedure-related risk factors (the duration of the investigation, non-dilatation of the bile duct, pancreatic duct opacification, EST, pancreatic EST, multiple cannulation attempts, gallstone extraction, bile duct dilatation, or stent implantation into the bile duct) demonstrated that there were no significant differences in the incidence of post-ERCP pancreatitis or hyperamylasaemia between the two groups (Table 4). There was likewise no significant difference in the incidence of pancreatitis between the two groups at the various endoscopic units. When the results at the individual endoscopic centres were compared, the only significant difference (*P* = 0.04) was that hyperamylasaemia occurred more often in the indomethacin group than in the control group in one of the 5 endoscopic units. There were no adverse events related to the use of indomethacin.

**DISCUSSION**

The pathomechanism of post-ERCP pancreatitis is multifactorial. The mechanical, hydrostatic, thermal, bacterial and chemical insults accompanying cannulation or and other modes of instrumentation of the papilla or the injection of contrast medium into the pancreatic duct may all result in a pancreatic duct injury. These initiating factors may act independently or in combination, leading to autodigestion due to the premature intracellular activation of pancreatic proteolytic enzymes and the release of inflammatory cytokines, producing both local and systemic effects[17]. The severity of pancreatitis is determined by the intensity of the inflammatory cascade and the systemic response. Attempts to prevent ERCP-induced pancreatitis take the pathogenetic factors into consideration are based upon mechanical and pharmacological approaches.

 Among the mechanical techniques applied short-term pancreatic stent placement has proved to be effective in reducing the incidence of post-ERCP pancreatitis[18,19]: in the initiation of post-ERCP pancreatitis, repeated cannulation attempts or prolonged manipulation around the papillary orifice play a considerable role through injury of the pancreatic sphincter, leading to oedema and mechanical obstruction. However, prophylactic stent placement appears to be of significant benefit only in experienced hands and only in patients at high risk of ERCP-induced pancreatitis. Moreover, it does not seem to be cost-effective in patients at average risk[20]. In the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, therefore, the use of prophylactic pancreatic stenting is recommended only for patients who are at high risk of developing pancreatitis after ERCP[21]. However, the risk of pancreatitis is not always easy to assess, and an unsuccessful cannulation attempt itself increases the risk of pancreatitis[22]. The search for effective pharmacological prophylactic agents therefore remains at the focus of clinical interest.

 Recent clinical trials suggested the promise of NSAIDs. Moreover, the administration of indomethacin or diclofenac in a single dose is simple, safe and inexpensive. However, our results did not confirm the conclusions of several single-centre studies as regards the prophylactic effectiveness of rectally administered NSAIDs. Our multicentre study involving 665 cases did not reveal any difference between indomethacin and placebo in the prophylaxis of post-ERCP pancreatitis/hyperamylasaemia. Our results are in accord with those of Cheon *et al*[12] and Senol *et al*[13], who investigated the possibility of the prophylactic effect of diclofenac administered intramuscularly or orally, respectively.

 In the first multicentre randomised controlled trial[23], which involved 602 patients, rectal indomethacin was found to reduce the incidence and severity of post-ERCP pancreatitis significantly. However, the indication in 82% of the cases in that study was a suspicion of a sphincter of Oddi dysfunction, and the results therefore the result cannot be extrapolated to all ERCP investigations. Furthermore, the majority of the patients received a prophylactic pancreatic stent, which can also result in the prevention of post-ERCP pancreatitis in such high-risk patients. The incidence of post-ERCP pancreatitis in the placebo group in our study was only 6.9%, while it was 16.9% in that of Elmunzer *et al*[23]; the main difference between the two trials was that our patients may be regarded as average-risk patients, in contrast with the high-risk patients in the study by Elmunzer *et al*[23]. Our results are in contrast with those of the recent meta-analysis by Yaghoobi *et al*[10], which included only 4 high-quality randomized controll trials published between 2007 and 2012[15,23,26,27], among them the study by Elmunzer *et al*[23], which supported the effectiveness of indomethacin for the prevention of post-ERCP pancreatitis. One appreciable difference between our study population and that of the meta-analysis was that the mean ages of the patients (44.4 ± 13.5, 58.4 ± 17.1 and 55.37 ± 18.0 in the study groups, and 46.0 ± 13.1, 58.1 ± 16.8 and 51.1 ± 17.0 in the control groups) in 3 of the 4 publications involved in the meta-analysis were much lower than those in our study (65.66 ± 16.21 in the indomethacin group, and 67.68 ± 15.56 in the control group), but it is unlikely that the different outcomes are explained solely by this difference. Our study may have certain limitations as concerns to allocation concealment, while the studies involved in the meta-analysis are somewhat heterogeneous as concerns the frequency of particular risk factors (*e.g.,* pancreatic duct injection), the use of a pancreatic stent and the timing of the administration of the suppository, which may influence the result.

 Despite the ESGE guideline recommendation that indomethacin or diclofenac may be administered rectally either before or after the endoscopic procedure[21], the time of the administration may theoretically also play a role in the prophylactic effectiveness. It appears relevant that protease inhibitors and agents that act by influencing the cytokine cascade proved effective in the treatment of experimental pancreatitis in animals, but did not influence the course of pancreatitis in humans. At the time of the therapeutic application in human patients, the cytokine cascade has already developed, whereas experimental pancreatitis is induced in animals only after or simultaneously with the administration of inhibitory agents. The peak plasma concentration of diclofenac or indomethacin is reached 30 min after their rectal administration[24]. Theoretically, therefore, rectal administration appears more reasonable before the ERCP investigation than after it. In our study, the patients received the suppository 10-15 min before the sedoanalgesic premedication for the ERCP. In a very recent study, when diclofenac in combination with somatostatin was given 30-60 min before the procedure, a significant decrease in the incidence of post-ERCP pancreatitis as compared with the control group was observed[25]. However, 5 previous studies which suggested the prophylactic effect of rectal NSAIDs did not uniformly support this theory because in 3 of them[11,26,27] the suppository was administered before, while in 2 of them[28,29] it was given after the investigation.

 The incidence of post-ERCP pancreatitis is strongly influenced by procedure-related risk factors, such as the expertise of the investigator, the number of cannulation attempts and the degree of filling of the pancreatic duct with contrast material, and also by the therapeutic procedures, in particular precut sphincterotomy and balloon dilatation of the sphincter. The indication of ERCP in the overwhelming majority of the cases is therapeutic intervention. In our study, EST was performed in 493 (74.1%) of 665 ERCPs. However, these figures do not represent the real proportion of the therapeutic interventions because previous biliary pancreatitis and sphincterotomy were regarded as exclusion criteria. The literature data indicate that a younger age, female gender, pancreatitis in the history, and a non-dilated common bile duct, with special regard to a sphincter of Oddi dysfunction are considered to be patient-related risk factors of post-ERCP pancreatitis[1,2,21]. Recent studies have suggested that obesity may serve as a prognostic indicator of a poor outcome in non-ERCP-induced acute pancreatitis. However, neither in our trial nor in a retrospective, multicentre study did obesity confer an increased risk of ERCP-induced pancreatitis[30]. In the subgroup analyses involving the patient- and procedure-related risk factors in our study, indomethacin did not prove to be effective in preventing post-ERCP pancreatitis. Although, differences in the study populations as a result of the randomisation may have influenced the outcome, the distributions of the risk factors in the two groups of patients did not differ significantly in our study.

 In summary, indomethacin administered rectally in a dose of 100 mg 10-15 min before the premedication for the ERCP procedure did not prove effective in preventing post-ERCP pancreatitis in our multicentre prospective randomised study.

**COMMENTS**

***Background***

Acute pancreatitis is the most common and potentially fatal complication of endoscopic retrograde cholangiopancreatography (ERCP). Non-steroidal anti-inflammatory drugs have been suggested to be effective in some prospective controlled trials, but the results are inconclusive.

***Research frontiers***

A number of pharmacological agents have been tested experimentally and in clinical trials for their effectiveness in preventing ERCP-induced pancreatitis. However, the majority of them proved to be ineffective or the results obtained were inconclusive.

***Innovations and breakthroughs***

Their multicentre prospective randomised study has demonstrated that indomethacin administered rectally in a dose of 100 mg 10-15 min before the premedication for the ERCP procedure did not prove effective in preventing post-ERCP pancreatitis.

***Applications***

This study provides important data demonstrating that the rectal application of indomethacin is not effective in preventing post-ERCP pancreatitis in average-risk patients.

***Terminology***

ERCP is a gastrointestinal endoscopic procedure, whith a considerable risk of complications. Indomethacin is a non-steroidal anti-inflammatory drug with analgesic, antipyretic and anti-inflammatory effects.

***Peer review***

This very interesting manuscript contributes new information to the literature regarding the use of rectal Indomethacin for prevention of post-ERCP pancreatitis. The results of this manuscript contradict previous studies in the literature.

**REFERENCES**

1 **Wang P**, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* 2009; **104**: 31-40 [PMID: 19098846 DOI: 10.1038/ajg.2008.5.]

2 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88 [PMID: 19286178 DOI: 10.1016/j.gie.2008.10.039]

3 **Wildenhain PM**, Melhem MF, Birsic WI, Sell HW, Rao KN. Acute hemorrhagic pancreatitis in mice: improved survival after indomethacin administration. *Digestion* 1989; **44**: 41-51 [PMID: 2599282]

4 **Elmunzer BJ**, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut* 2008; **57**: 1262-1267 [PMID: 18375470 DOI: 10.1136/gut.2007.140756]

5 **Zheng MH**, Xia HH, Chen YP. Rectal administration of NSAIDs in the prevention of post-ERCP pancreatitis: a complementary meta-analysis. *Gut* 2008; **57**: 1632-1633 [PMID: 18941015]

6 **Dai HF**, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2009; **8**: 11-16 [PMID: 19208508]

7 **Ding X**, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. *Gastrointest Endosc* 2012; **76**: 1152-1159 [PMID: 23164513 DOI: 10.1016/j.gie.2012.08.021]

8 **Yuhara H**, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T, Mine T. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: protease inhibitors and NSAIDs in a meta-analysis. *J Gastroenterol* 2014; **49**: 388-399 [PMID: 23720090]

9 **Akbar A**, Abu Dayyeh BK, Baron TH, Wang Z, Altayar O, Murad MH. Rectal nonsteroidal anti-inflammatory drugs are superior to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a network meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 778-783 [PMID: 23376320 DOI: 10.1016/j.cgh.2012.12.043]

10 **Yaghoobi M**, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, Szego P, Barkun AN. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. *Aliment Pharmacol Ther* 2013; **38**: 995-1001 [PMID: 24099466 DOI: 10.1111/apt.12488]

11 **Otsuka T**, Kawazoe S, Nakashita S, Kamachi S, Oeda S, Sumida C, Akiyama T, Ario K, Fujimoto M, Tabuchi M, Noda T. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial. *J Gastroenterol* 2012; **47**: 912-917 [PMID: 22350703 DOI: 10.1007/s00535-012-0554-7]

12 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. *Gastrointest Endosc* 2007; **66**: 1126-1132 [PMID: 18061712]

13 **Senol A**, Saritas U, Demirkan H. Efficacy of intramuscular diclofenac and fluid replacement in prevention of post-ERCP pancreatitis. *World J Gastroenterol* 2009; **15**: 3999-4004 [PMID: 19705494]

14 **Dumonceau JM**, Rigaux J, Kahaleh M, Gomez CM, Vandermeeren A, Devière J. Prophylaxis of post-ERCP pancreatitis: a practice survey. *Gastrointest Endosc* 2010; **71**: 934-99, 934-99, [PMID: 20226455 DOI: 10.1016/j.gie.2009.10.055]

15 **Döbrönte Z**, Toldy E, Márk L, Sarang K, Lakner L. [Effects of rectal indomethacin in the prevention of post-ERCP acute pancreatitis]. *Orv Hetil* 2012; **153**: 990-996 [PMID: 22714033 DOI: 10.1556/OH.2012.29403]

16 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995]

17 **Karne S**, Gorelick FS. Etiopathogenesis of acute pancreatitis. *Surg Clin North Am* 1999; **79**: 699-710 [PMID: 10470320]

18 **Mazaki T**, Masuda H, Takayama T. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. *Endoscopy* 2010; **42**: 842-853 [PMID: 20886403 DOI: 10.1055/s-0030-1255781]

19 **Sofuni A**, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, Toyota M, Fujii T, Harada Y, Takada T. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol* 2007; **5**: 1339-1346 [PMID: 17981247]

20 **Das A**, Singh P, Sivak MV, Chak A. Pancreatic-stent placement for prevention of post-ERCP pancreatitis: a cost-effectiveness analysis. *Gastrointest Endosc* 2007; **65**: 960-968 [PMID: 17331513]

21 **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]

22 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864 [PMID: 15173799]

23 **Elmunzer BJ**, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1414-1422 [PMID: 22494121 DOI: 10.1056/NEJMoa1111103]

24 **Tammaro S**, Caruso R, Pallone F, Monteleone G. Post-endoscopic retrograde cholangio-pancreatography pancreatitis: is time for a new preventive approach? *World J Gastroenterol* 2012; **18**: 4635-4638 [PMID: 23002332]

25 **Katsinelos P**, Fasoulas K, Paroutoglou G, Chatzimavroudis G, Beltsis A, Terzoudis S, Katsinelos T, Dimou E, Zavos C, Kaltsa A, Kountouras J. Combination of diclofenac plus somatostatin in the prevention of post-ERCP pancreatitis: a randomized, double-blind, placebo-controlled trial. *Endoscopy* 2012; **44**: 53-59 [PMID: 22198776]

26 **Sotoudehmanesh R**, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. *Am J Gastroenterol* 2007; **102**: 978-983 [PMID: 17355281]

27 **Montaño Loza A**, Rodríguez Lomelí X, García Correa JE, Dávalos Cobián C, Cervantes Guevara G, Medrano Muñoz F, Fuentes Orozco C, González Ojeda A. [Effect of the administration of rectal indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes]. *Rev Esp Enferm Dig* 2007; **99**: 330-336 [PMID: 17883296]

28 **Murray B**, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; **124**: 1786-1791 [PMID: 12806612]

29 **Khoshbaten M**, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. *J Gastroenterol Hepatol* 2008; **23**: e11-e16 [PMID: 17683501]

30 **Deenadayalu VP**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Temkit M, Lehman GA, Sherman S. Does obesity confer an increased risk and/or more severe course of post-ERCP pancreatitis?: a retrospective, multicenter study. *J Clin Gastroenterol* 2008; **42**: 1103-1109 [PMID: 18936645 DOI: 10.1097/MCG.0b013e318159cbd1]

**P-Reviewers:** Barkin JA, He SB **S-Editor:** Gou SX  **L-Editor: E-Editor:**

**Table 1 Comparison of the two groups of patients according to patient and investigation characteristics (*n* = 665) *n* (%)**

|  |  |  |
| --- | --- | --- |
| **Patient and investigation** **characteristics** | **Indomethacin group****(*n* = 347)** | **Control group****(*n* = 318)** |
| Gender Male (*n* = 239) | 133 (55.64) | 106 (44.35) |
|  Female (*n* = 426) | 214 (50.23) | 212 (49.76) |
| Age < 70 yr (*n* = 355) | 190 (53.52) | 165 (46.48) |
|  >70 yr (*n* = 310) | 157 (50.65) | 153 (49.35) |
| BMI < 25 (*n* = 303) | 156 (51.48) | 147 (48.51) |
|  25-30 (*n* = 236) | 125 (53.96) | 111 (47.03) |
|  > 30 (*n* = 126) | 66 (52.38) | 60 (47.62) |
| Duration of ERCP  |  |  |
|  < 20 min (*n* = 454) | 236 (52.0) | 218 (48.0) |
|  >20 min (*n* = 211) | 111 (52.6) | 100 (47.4) |
| Dilated/non-dilated bile duct |  |  |
|  dilated (*n* = 366) | 189 (51.64) | 177 (48.36) |
|  non-dilated (*n* = 299) | 158 (52.84) | 141 (47.15) |
| Pancreatic duct opacification (*n* = 463)  | 246 (53.13) | 217 (46.87) |
| EST Biliary (*n* = 443) | 224 (50.56) | 219 (49.43) |
|  Pancreatic/double (*n* = 48)  | 22 (44.0) | 28 (56.0) |
| Difficult cannulation (*n* = 116) | 64 (55.17) | 52 (44.83) |
| Gallstone extraction (*n* = 165) | 82 (49.7) | 83 (50.3) |
| Bile duct dilatation (*n* = 22) | 11 (50.0) | 11 (50.0) |
| Biliary stent placement |  |  |
|  Plastic stent (*n* = 75) | 35 (46.7) | 40 (53.3) |
|  Metal stent | 0 | 0 |

BMI: Body mass index; EST: Endoscopic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 2 Distribution of the specific risk factors in the investigated population (*n* = 665) *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk factors** | **Indomethacin****group (*n* = 347)** | **Control group****(*n* = 318)** | ***P* value** |
| Age < 50 yr (*n* = 104) | 57/347 (16.4) | 47/318 (14.8) | 0.559 |
| Female gender (*n* = 426) | 214/347 (61.7) | 212/318 (66.7) | 0.180 |
| BMI > 25 (*n* = 362) | 191/347 (55.0) | 171/318 (53.8) | 0.743 |
| Duration of ERCP |  |  |  |
|  > 20 min (*n* = 211) | 111/347 (32.0) | 100/318 (31.4) | 0.880 |
| Non-dilated bile duct (*n* = 299) | 158/347 (45.5) | 141/318 (44.3) | 0.757 |
| Pancreatic duct opacification | 246/347 (70.1) | 217/318 (68.2) | 0.534 |
|  (*n* = 463)  |  |  |  |
| EST biliary (*n* = 443) | 224/347 (64.6) | 219/318 (68.9) | 0.195 |
| EST pancreatic/double (*n* = 48) | 20/347 (5.8) | 28/318 (8.8) | 0.130 |
| Difficult cannulation (*n* = 116) | 64/347 (18.4) | 52/318 (16.4) | 0.111 |
| Gallstone extraction (*n* = 165) | 82/347 (23.6) | 83/318 (26.1) | 0.461 |
| Bile duct dilatation (*n* = 22) | 11/347 (3.2) | 11/318 (3.5) | 0.835 |
| Biliary plastic stent placement | 35/347 (10.1) | 40/318 (12.6) | 0.640 |
|  (*n* = 75) |  |  |  |
| Total (*n* = 2734) | 1413/4164 (33.9) | 1321/3816 (34.6) | 0.520 |

BMI: Body mass index; EST: Endoscopic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 3 Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis and hyperamylasaemia (*n* = 665)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group of patients** | **ERCP (*n*)** | **Pancreatitis (*n*)** | **Pancreatitis (*n*)** | **Hyperamylasaemia (*n*)** | **Hyperamylasaemia (*n*)** |
| Indomethacin | 347 | 20 (mild: 16, severe: 4) | 5.76 | 81 | 23.34 |
|  Control | 318 | 22 (mild: 18, severe: 4) | 6.92 | 79 | 24.84 |
| Total | 665 | 42 | 6.32 | 160 | 24.06 |

There were no statistically significant differences (*P* = 0.541 and *P* = 0.651). ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 4 Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis according to risk factors (*n* = 665) *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk factors** | **Indomethacin****group (*n*)** | **Control group****(*n*)** | ***P* value** |
| Age < 50 yr (*n* = 104) | 5/57 (8.77) | 6/47 (12.76) | 0.365 |
| Female gender (*n* = 426) | 16/214 (7.47) | 19/212 (8.96) | 0.576 |
| BMI > 25 (*n* = 362) | 12/191 (6.28) | 10/171 (5.85) | 0.862 |
| Duration of ERCP |  |  |  |
|  > 20 min (*n* = 211) | 8/111 (7.2) | 7/100 (7.0) | 0.58 |
| Non-dilated bile duct (*n* = 299) | 10/158 (6.33) | 11/141 (7.8) | 1.00 |
| Pancreatic duct opacification | 20/246 (8.13) | 20/217 (9.21) | 0.263 |
|  (*n* = 463)  |  |  |  |
| EST biliary (*n* = 443) | 14/224 (6.25) | 14/219 (6.4) | 0.951 |
| EST pancreatic/double (*n* = 48) | 4/20 (20.0) | 5/28 (17.86) | 0.56 |
| Difficult cannulation (*n* = 116) | 4/64 (6.25) | 6/52 (11.54) | 0.478 |
| Gallstone extraction (*n* = 165) | 3/82 (3.66) | 5/83 (6.02) | 0.451 |
| Bile duct dilatation (*n* = 22) | 1/11 (9.1) | 2/11 (18.2) | 0.537 |
| Biliary plastic stent placement (*n* = 75) | 4/35 (11.43) | 3/40 (7.5) | 0.58 |

There were no statistically significant differences. BMI: Body mass index; EST: Endoscopic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography.