World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i29.10151

World J Gastroenterol 2014 August 7; 20(29): 10151-10157
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

RANDOMIZED CONTROLLED TRIAL

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

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Supported by TÁMOP-4.2.2.A-11/1/KONV-2012-0035 and OTKA K101521
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Received: January 12, 2014 Revised: March 12, 2014
Accepted: April 21, 2014
Published online: August 7, 2014

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 five 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 because of 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 eight (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 prove effective in preventing post-ERCP pancreatitis.

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 five endoscopic units. The results for 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; 20(29): 10151-10157 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i29/10151.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i29.10151

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%; however, this can rise to 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 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 in 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, leukotrienes 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 been reported to decrease the mortality resulting from experimental pancreatitis in animals[3].

Three meta-analyses involving the data of four earlier randomised controlled trials indicated that indomethacin or diclofenac administered rectally 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; the intergroup differences in the timing, type and route of NSAID administration; the heterogeneity in the proportion of high-risk patients; and the prophylactic placement of pancreatic stents. The benefits of multicentre 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 centres 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 two other randomised controlled trials diclofenac 50 mg orally or 75 mg intramuscularly was concluded to be non-effective[12,13]. Therefor, there is some doubt as to the clinical effectiveness of NSAIDs in the prophylaxis of post-ERCP pancreatitis, all the more so as several agents have shown promise in early single-centre studies; however, 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 five endoscopic units (tertiary refer-

ral centres for therapeutic endoscopy) on 686 patients who consecutively underwent ERCP within inpatient care, in two centres between January 2012 and January 2013 and in three 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 Paris, France) or an identical-appearing suppository containing the inert vehicle 10-15 min before the sedoanalgesic premedication for ERCP. An independent endoscopic nurse supervised the suppository administration and its retention within the rectal ampulla, and completed the list detailing the patient's characteristics. An investigator who was unaware of the nature of the given suppository recorded the investigation characteristics. 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. 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 three 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 d, 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 was more than five 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 Regional/Local Research Ethical Committees approved the study ethically. 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 Ingelheim, Ingelheim am Rhein, Germany) was used for the control of hyperperistalsis at the discretion of the endoscopist. For cholangiopancreatography, the iodine-containing contrast material lysine amidotrizoate (Peritrast 600 mg/mL, Dr. Köhler F Chemie GmbH, Bensheim, Germany) 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 χ^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 were excluded from the evaluation because of the incompleteness of their data, and seven 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, body mass index (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 was 66.62 ± 15.92 (SD) years: 65.66 ± 16.21 years (SD) in the indomethacin group and 67.68 ± 15.56 years (SD) in the control group.

Post-ERCP pancreatitis

Post-ERCP pancreatitis developed 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) ($P = 0.54$) (Table 3). Sixteen (4.6%) cases of mild and four (1.2%) of severe pancreatitis occurred in the indomethacin group, and 18 (5.7%) of mild and four (1.3%) of severe pancreatitis in the placebo group. Hyperamylasaemia developed in 160 (24.1%) patients overall: 81 (23.3%) in the study group, and 79 (24.1%) in the control group ($P = 0.65$) (Table 3). In the placebo group, one patient died 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, mul-

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.

tiple 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 five endoscopic units. There were no adverse events related to the use of indomethacin.

DISCUSSION

The pathological mechanism of post-ERCP pancreatitis is multifactorial. The mechanical, hydrostatic, thermal, bacterial and chemical insults accompanying cannulation and/or 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 because of 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 and are based upon mechanical and pharmacological approaches.

Table 2 Distribution of 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 (*n* = 463)	246/347 (70.1)	217/318 (68.2)	0.534
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 (*n* = 75)	35/347 (10.1)	40/318 (12.6)	0.640
Total (*n* = 2734)	1413/4164 (33.9)	1321/3816 (34.6)	0.520

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

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 prophylac-

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

Group of patients	ERCP (*n*)	Pancreatitis (*n*)	Pancreatitis	Hyperamylasaemia (*n*)	Hyperamylasaemia
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	Control group	*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)	0.580
Non-dilated bile duct (*n* = 299)	10/158 (6.33)	11/141 (7.8)	1.000
Pancreatic duct opacification (*n* = 463)	20/246 (8.13)	20/217 (9.21)	0.263
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)	0.560
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)	0.580

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

tic 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 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 might be regarded as average-risk patients, in contrast with the high-risk patients in the other study. Our results are in contrast with those of the recent meta-analysis by Yaghoobi *et al*[10], which included only four high-quality randomized controll trials published between 2007 and 2012[15,23-25], 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 years in the study groups, and 46.0 ± 13.1, 58.1 ± 16.8 and 51.1 ± 17.0 years in the control groups) in three of the four 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); however, 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 in terms of 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[26]. 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[27]. However, five previous studies that suggested

the prophylactic effect of rectal NSAIDs did not uniformly support this theory because in three of them[11,23,24], the suppository was administered before, while in two 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. It is also affected 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 our subgroup analyses involving the patient- and procedure-related risk factors, 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

This 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 with 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 the prevention of post-ERCP pancreatitis. The results of this manuscript contradict previous studies in the literature.

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P- Reviewer: Barkin JA, He SB **S- Editor**: Gou SX
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ISSN 1007-9327