Pharmacological prophylaxis versus pancreatic duct stenting plus pharmacological prophylaxis for prevention of post-ERCP pancreatitis in high risk patients: a randomized trial

Authors
Rasoul Sotoudehmanesh1,2, Ali Ali-Asgari1,2, Morteza Khatibian1,2, Mehdi Mohamadnejad1,3, Shahin Merat1,2,3, Anahita Sadeghi1,2, Abbas Keshtkar4, Mohammad Bagheri1,2, Alireza Delavari1,2, Mohammad Amani1,2, Homayoon Vahedi1,2, Siavosh Nasser-Moghaddam1,2,3, Alireza Sima1,2, Mohammad A. Eloubeidi5, Reza Malekzadeh1,2,3

Institutions
1 Liver and Pancreaticobiliary Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
2 Digestive Disease Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
3 Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
4 Department of Health Science Educational Development, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
5 Anniston Digestive Health, Anniston, Alabama, United States

submitted 4.2.2019
accepted after revision 14.6.2019

Bibliography
DOI https://doi.org/10.1055/a-0977-3119
Published online: 27.8.2019 | Endoscopy 2019; 51: 915–921
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
Rasoul Sotoudehmanesh, MD, Liver and Pancreaticobiliary Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Shariati Hospital, Kargar Shomali Avenue, Tehran, Iran
Fax: +98-21-82415400
sotoudehmanesh@tums.ac.ir

Scan this QR-Code for the author's interview.

ABSTRACT

Background Acute pancreatitis is a serious complication of endoscopic retrograde cholangiopancreatography (ERCP). The aim of this noninferiority study was to evaluate the effectiveness of pancreatic duct (PD) stenting plus pharmacological prophylaxis vs. pharmacological prophylaxis alone in the prevention of post-ERCP pancreatitis (PEP) in high risk patients.

Methods In this randomized, controlled, double-blind, noninferiority trial, patients at high risk of developing PEP were randomly allocated to pharmacological prophylaxis (rectal indomethacin, sublingual isosorbide dinitrate, and intravenous hydration with Ringer’s lactate) plus PD stenting (group A) or pharmacological prophylaxis alone (group B). The rate and severity of PEP, serum amylase levels, and length of hospital stay after ERCP were assessed.

Results During 21 months, a total of 414 patients (mean age 55.5 ± 17.0 years; 60.2 % female) were enrolled (207 in each group). PEP occurred in 59 patients (14.3 %, 95 % confidence interval [CI] 11.1 %–17.9 %: 26 patients [12.6 %, 95 %CI 8.6 %–17.6 %] in group A and 33 [15.9 %, 95 %CI 11.4 %–21.4 %] in group B). There was no significant difference between the two groups in PEP severity (P = 0.59), amylase levels after 2 hours (P = 0.31) or 24 hours (P = 0.08), and length of hospital stay after ERCP were assessed.

Conclusions The study failed to demonstrate noninferiority or inferiority of pharmacological prophylaxis alone compared with PD stenting plus pharmacological prophylaxis in the prevention of PEP in high risk patients.

Clinical.Trials.gov
NCT02368795
Randomized, double-blind, controlled, single centre, noninferiority trial NCT02368795 at clinicaltrials.gov

Introduction

Acute pancreatitis is a serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) occurs in 9%–42% of patients, depending on risk factors and indications of ERCP. Although most cases of PEP are mild or moderately severe, severe and/or necrotizing pancreatitis with substantial morbidity and mortality can occur [1, 2].
Known mechanisms of PEP include impaired drainage of the pancreatic duct (caused by edema and/or spasm of the sphincter of Oddi), activation of phospholipase A2 leading to activation of prostaglandin and prostacyclin cascades, and ischemia of the pancreatic tissue. Many strategies have been suggested for preventing PEP, and can be categorized into mechanical (pancreatic duct [PD] stenting) and pharmacological prophylaxis. PD stenting probably maintains pancreatic drainage that may be impaired by papillary edema or spasm of the sphincter of Oddi during ERCP. Based on previous studies, the majority of endoscopists insert a “fall out” stent into the PD in high risk patients [3, 4].

The effectiveness of rectally administered nonsteroidal anti-inflammatory drugs (NSAIDs) for the prevention of PEP has also been demonstrated in previous studies [5–7]; as a result, routine rectal administration of 100 mg of indomethacin during ERCP is recommended for the prevention of PEP in high risk patients. Nitrates may also have a role in preventing PEP [8, 9]. The efficacy of adequate hydration with lactated Ringer’s solution has also been shown in recent studies to decrease PEP [10, 11].

Most trials that have assessed the effectiveness of PD stenting in patients at high risk of PEP were designed before these pharmacological measures became available. The aim of this study, therefore, was to assess the noninferiority of PD stenting plus pharmacological prophylaxis vs. pharmacological prophylaxis alone in the prevention of PEP among high risk patients.

Methods

Study design
The study was designed as a randomized, double-blind, controlled, single-centre, noninferiority trial (NCT02368795 at clinicaltrials.gov). We enrolled consecutive consenting patients who were referred for ERCP at the endoscopy unit of Shariati Hospital, a tertiary referral center at the Tehran University of Medical Sciences (Tehran, Iran). The trial was registered at ClinicalTrials.gov (NCT02368795, November 2015).

Participants
We invited patients over 15 years of age who were at increased risk of developing PEP to participate in the clinical trial (Table 1). Patients were considered at high risk of developing PEP based on a modification of the criteria defined in previous studies [12, 13]. We defined “high risk” as having at least one major or two minor risk factors for PEP (Table 1). Exclusion criteria are given in Table 2. The study was approved by the Institutional Review Board of the Digestive Disease Research Institute of Tehran University of Medical Sciences, according to the declaration of Helsinki. Informed consent was also obtained according to the guidelines of the institute.

Randomization and masking
Block-balanced randomization was used to allocate patients to either group A or group B with a block size of 2. A statistician developed block-balanced sequences based on computer-generated random numbers. The allocation was concealed by use of sealed envelopes. The envelopes were opened by the physicians who completed the questionnaires immediately before the procedure or during the procedure as soon as eligibility criteria were satisfied. Participants and the physicians assessing the outcome were blinded to group assignment. The endoscopists involved in ERCP or removal of PD stents were aware of patient allocation but were not involved in post-procedure patient care, the outcomes assessment or analysis of data.

Interventions
Eligible patients were randomly assigned to one of two groups: group A received pharmacological prophylaxis plus PD stenting (5 Fr, 4 cm, single-pigtail; Endoflex GmbH, Voerde, Germany); group B received pharmacological prophylaxis alone. Pharmacological prophylaxis in both groups consisted of 100 mg indomethacin given rectally and 5 mg sublingual isosorbide dinitrate, given 5 minutes before the procedure. Both groups also received infusion of Ringer’s lactate 6 mL/kg/h during the procedure, followed by a 20 mL/kg bolus after the ERCP and 3 mL/kg for 8 additional hours.

Patients underwent intraprocedural deep sedation with propofol and fentanyl under the supervision of a certified anesthesiologist. ERCP was performed by gastroenterology fellows-in-training under direct supervision of expert endoscopists. All patients were closely observed in the recovery room of the endoscopy unit for 24 hours after ERCP. Patients who required more than 24 hours of hospitalization were transferred to the gastroenterology ward.

Fluoroscopy for assessing spontaneous stent migration was performed 3 days after PD stenting. Patients with the PD stent still in place underwent endoscopic removal.

Outcomes
The primary outcome was the rate of PEP. Secondary outcomes included the severity of PEP, length of hospital stay, and post-ERCP amylase levels.
PEP was defined as a serum amylase level more than three times the upper limit of normal with associated epigastric pain and tenderness within 24 hours after ERCP. The severity of PEP was graded as mild, moderate, or severe based on a consensus definition by Cotton et al. [14]. Serum amylase was determined 2 hours after ERCP in all patients. If it was more than three times the upper limit of normal (100 IU/L) and the patient developed abdominal pain or nausea and vomiting, he/she was kept fasting and maintained on intravenous fluids and opiate analgesics. The next morning, serum amylase assessment was repeated, and all patients were interviewed and examined in order to assess for evidence of acute pancreatitis.

Sphincter of Oddi dysfunction (SOD) was defined according to the modified Milwaukee biliary group classification [15].

Manometry of the sphincter of Oddi was not performed, and patients with suspicion of SOD were treated empirically with sphincterotomy. Significant hemorrhage was defined as bleeding requiring blood transfusion or endoscopic, radiological, and/or surgical intervention.

Statistical analysis

Using the assumptions of a significance level of 0.05, a PEP rate of 10% in group A and 15% in group B, with a noninferiority margin of 5%, we calculated that 187 participants were required to be enrolled in each study group in order to achieve 80% power for determining whether the rate of PEP in group B was noninferior to that in group A. We finally enrolled a total of 207 patients in each group to allow for possible loss to follow-up or patients not evaluable for the primary outcome. Noninferiority for the primary efficacy end point was established if the upper bound of the 95% confidence interval (CI) for the difference in proportion of participants with PEP between the groups was less than 5.0%.

Categorical variables were described using proportions and two-sided 95% CIs. Continuous variables with normal distribution were reported using mean and standard deviation (SD). Variables with non-normal distribution were expressed as median and interquartile range (IQR).

The rate of PEP between the groups was compared using the chi-squared or Fisher’s exact test for qualitative variables. The Mann-Whitney U test was used to compare median serum amylase levels between the two groups. A P value of 0.05 or less was considered statistically significant. All analyses were performed using SPSS 20.0 statistical software (IBM Corp., Armonk, New York, USA).

All analyses were done according to the primary analysis plan in the protocol, except for a post hoc analysis that was conducted to determine differences in the rates of PEP in subgroups of patients with difficult cannulation, deep PD guidewire cannulation, and needle-knife sphincterotomy. The latter analysis was suggested after inconclusive results were observed in the primary outcomes.

Results

From November 2015 to August 2017, 2114 patients were referred to the Tehran Shariati Hospital for ERCP. A total of 414 patients (mean age 55.5 ± 17.0 years; 60.2% female) met the eligibility criteria (high risk of PEP) and agreed to enroll in the study; reasons for exclusion are shown in Fig. 1. The baseline characteristics of participants are summarized in Table 3.

For all patients who developed PEP, the diagnosis was established within 24 hours after ERCP. PEP occurred in 26 patients (12.6%, 95%CI 8.6%–17.6%) in group A and 33 (15.9%, 95%CI 11.4%–21.4%) in group B. One of the 13 patients in whom PD stenting failed developed PEP.

### Table 2 Exclusion criteria.

| Low risk of PEP | History of biliary sphincterotomy Routine biliary stent exchange Chronic pancreatitis |
| Study interventions not possible/contraindicated | Surgically altered anatomy (Billroth II gastrectomy or Roux-en-Y anastomosis) Tumor of ampulla of Vater Uncontrolled coagulopathy Unable to tolerate indomethacin (creatinine level > 1.4 mg/dl or active peptic ulcer disease), pregnancy or breastfeeding Unable to tolerate nitrates (closed-angle glaucoma) Unable to tolerate aggressive hydration (cardiac insufficiency: NYHA functional class II or higher, renal insufficiency, electrolyte disturbances, clinical signs of fluid overload including peripheral or pulmonary edema, liver dysfunction with varix > F1, or respiratory insufficiency) |
| Conditions with confounding effects on outcome | Regular NSAID use during the preceding week Acute pancreatitis at the time of ERCP |
| Patients requiring PD drainage | ERCP to bridge dominant strictures, bypass obstructing PD stones, drain pseudocysts, seal duct disruptions, pancreatic head cancer with main PD obstruction, IPMN or pancreas divisum; known main PD stricture toward the head of the pancreas |
| Others | Age younger than 15 years Refusal to participate in the study |

PEP, post-ERCP pancreatitis; NYHA, New York Heart Association; NSAID, nonsteroidal anti-inflammatory drug; ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct; IPMN, intraductal papillary mucinous neoplasm.
PD stenting was attempted in all patients in group A, but failed in 13 patients (6.3%). Among participants with successful PD stent placement (n = 194), the stents had spontaneously passed within 3 days in 22 cases (11.3%) and were removed endoscopically in the remaining 172 cases (88.7%).

At 2 hours after ERCP, median serum amylase levels were similar in the two groups (median 93.5 IU/L [IQR 61.0–155.7] in group A and 77.0 IU/L [IQR 51.5–187.0] in group B; P = 0.31). Serum amylase levels after 24 hours were also not significantly different between the two groups (median 119.0 IU/L [IQR 72.0–270.0] in group A and 96.0 IU/L [IQR 55.5–263.0] in group B; P = 0.08).

In group A, PD injection of contrast (only a few milliliters and not enough to cause acinarization) was done to confirm the correct placement of the guidewire in 22 patients (10.6%, 95% CI 6.8%–15.7%) before placing the PD stent. In nine patients in group B (4.3%, 95% CI 2.0%–8.1%) the PD duct was injected inadvertently.

The severity of pancreatitis was not different between the two groups (P = 0.59): in group A, there were 22 (10.6%, 95% CI 6.8%–15.7%) mild and 4 (1.9%, 95% CI 0.5%–4.9%) moderate to severe cases of pancreatitis; in group B, there were 27 (13.0%, 95% CI 8.8%–18.4%) mild and 6 (2.9%, 95% CI 1.1%–6.2%) moderate to severe pancreatitis.

In group A, the rate of PEP was not statistically different between patients with PD guidewire entry (n = 102), (12.4%, 95% CI 6.8%–20.2% vs. 12.7%, 95% CI 6.9%–20.8%).

The length of hospital stay was not significantly different between the two groups (median 1.0 day [IQR 1.0–2.0] in group A and 1.0 [IQR 1.0–1.0] in group B; P = 0.07).

Following ERCP, some adverse events (other than pancreatitis) were observed: a significant hemorrhage at the sphincterotomy site in two cases (0.5%), retroperitoneal perforation in 4 (1.0%), and fever in 22 cases (5.3%). All complications were managed conservatively.

There were no adverse events attributable to the pharmacological prophylaxis (indomethacin suppository, sublingual isosorbide, and Ringer’s lactate solution) or mechanical prophylaxis (PD stenting) in any patient. There were no deaths attributed to PEP.

▶ Fig.2 shows the differences in PEP by intention-to-treat analysis in subgroups of patients with difficult cannulation, deep PD guidewire cannulation, and needle-knife sphincterotomy.

Discussion

The noninferiority design was selected for this study because if pharmacological prophylaxis was demonstrated to be equally effective, it offers several advantages over PD stenting. These advantages include easier and single administration of pharmacological prophylaxis, a lower risk of complications, and favor-
able cost-effectiveness. However, the study failed to demonstrate noninferiority or inferiority of pharmacological prophylaxis alone compared with PD stenting plus pharmacological prophylaxis in preventing PEP among patients at high risk.

Several studies have supported the benefits of prophylactic PD stenting for the prevention of PEP, with most reporting that PD stenting is effective [16–18]; therefore, PD stenting is recommended by consensus guidelines, particularly for high risk patients [19–21].

Alternatively, several randomized controlled trials have confirmed the efficacy of rectal indomethacin in the prevention of PEP [22–24]; as a result, routine rectal administration of 100 mg of indomethacin immediately before or after ERCP is recommended to minimize the risk of PEP in high risk patients.

### Table 3 Baseline characteristic of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Group B&lt;sup&gt;2&lt;/sup&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>53.9 (16.8)</td>
<td>56.8 (17.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>131 (63.3)</td>
<td>120 (58.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>History of PEP, n (%)</td>
<td>3 (1.5)</td>
<td>0 (0.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Difficult cannulation, n (%)</td>
<td>146 (70.5)</td>
<td>138 (66.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>&gt; 1 deep PD guidewire cannulation, n (%)</td>
<td>54 (26.1)</td>
<td>47 (22.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Needle-knife sphincterotomy, n (%)</td>
<td>47 (22.7)</td>
<td>48 (23.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Time for cannulation, median (IQR), minutes</td>
<td>10.0 (5.0–20.0)</td>
<td>10.0 (4.0–15.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Indication for ERCP, n (%)</td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>• CBD stone</td>
<td>150 (72.5)</td>
<td>150 (72.5)</td>
<td></td>
</tr>
<tr>
<td>• SOD</td>
<td>9 (4.3)</td>
<td>11 (5.3)</td>
<td></td>
</tr>
<tr>
<td>• CBD tumor</td>
<td>13 (6.3)</td>
<td>11 (5.3)</td>
<td></td>
</tr>
<tr>
<td>• Pancreatic tumor</td>
<td>5 (2.4)</td>
<td>9 (4.3)</td>
<td></td>
</tr>
<tr>
<td>• Post-surgical complications</td>
<td>2 (1.0)</td>
<td>8 (3.9)</td>
<td></td>
</tr>
<tr>
<td>• Others</td>
<td>18 (8.7)</td>
<td>28 (13.5)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; PEP, post-ERCP pancreatitis; PD, pancreatic duct; IQR, interquartile range; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; SOD, sphincter of Oddi dysfunction.

<sup>1</sup> Pharmacological prophylaxis plus PD stenting.

<sup>2</sup> Pharmacological prophylaxis alone.

### Fig. 2 Differences (95% confidence intervals) in the rates of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) in high risk patients receiving pharmacological prophylaxis with and without pancreatic duct (PD) stenting (n = 414). CI, confidence interval; RD, risk difference.
The influence of sublingual nitrates on the reduction of PEP has also been assessed in previous studies [25, 26].

Despite the effectiveness of PD stenting in PEP prophylaxis, there are a few disadvantages. PD stenting is a time-consuming procedure, is technically challenging, and placement failure may result in an increased risk of PEP [27–29]. The other disadvantage is that PD stenting adds to the already high cost of ERCP [29]. Furthermore, removing the stent requires another visit for the patient, fluoroscopy, and in a portion of cases, endoscopic removal of the stent, which further add to the costs of this approach. Another important adverse event associated with PD stenting is stent migration. Spontaneous passage may lead to a loss of any beneficial effect the stent might have. Upstream migration (into the PD), though rare, is usually a serious adverse event resulting in stent-induced PD changes (especially in a normal PD), the need for several endoscopic attempts to retrieve the stent, and, occasionally, a surgical intervention when ERCP retrieval fails.

The core studies that established the role of PD stenting in the prevention of PEP compared a prophylactic stent with a control group that did not receive any pharmacological prophylaxis [17, 18, 30]. In a recent network meta-analysis, Akbar found rectal NSAIDs to be superior to PD stenting for the prevention of PEP [31].

The rate of failed PD stenting in our study was 6.3%, which is similar to the rate reported in other studies [17, 28]. Failed PD stenting may lead to a worse outcome for patients compared with those who do not undergo attempted PD stenting. Choksi et al. [28] reported a PEP rate of 34.7% in patients who did not receive indomethacin and had failed PD stenting, a rate that was significantly greater than the PEP rates in patients who did not undergo (attempted) PD stenting or in whom PD stenting was successful [26]. Similar findings were reported by Elmunzer et al. [29].

Most of the studies of PD stenting for the prevention of PEP were conducted before the widespread use of pharmacological prophylaxis including indomethacin suppository for this indication.

To the best of our knowledge, this study is the first noninferiority, randomized controlled trial to assess the added benefit of PD stenting combined with pharmacological prophylaxis for the prevention of PEP among high risk patients. Demonstration of noninferiority of pharmacological prophylaxis might be sufficient to recommend this strategy as the primary method for prevention of PEP in high risk groups, because this approach is effective, simple to use, inexpensive, safe, and with minimal limitations. However, this study was inconclusive for the main outcome, as noninferiority could not be demonstrated; the study may also have been underpowered. Furthermore, the post hoc subgroup analyses of patients with difficult cannulation, deep PD guidewire cannulation, and needle-knife sphincterotomy, found no significant differences in PEP between the two groups.

Our results should be interpreted in the context of the limitations. The European Society of Gastrointestinal Endoscopy [20] and the American Society for Gastrointestinal Endoscopy [21] guidelines have identified independent risk factors for the development of PEP; however, these factors may pose varying degrees of risk. Although clinical practice guidelines make general recommendations on PEP prevention in high risk patients, there is no consensus on strict eligibility criteria for clinical trials of PEP prevention. This problem results in heterogeneity between studies that limits both the generalizability of results and comparison between studies. Our study was performed in the setting of a single referral center with fellows-in-training involved in all procedures. Complexity of patients and experience of the endoscopist play important roles in the outcome of ERCP and such differences in settings further limit the generalizability of our study. To overcome this problem, our eligibility criteria were similar to those used in the study by Elmunzer et al. [23], and similar criteria are being used in a multicenter study comparing PD stents with rectal indomethacin alone (SVI study), which is currently recruiting patients (ClinicalTrials.gov: NCT02476279). It takes a long time to recruit a sufficient number of high risk patients to ensure a sample size that has adequate statistical power to reach conclusive results. As a result, our sample size might have been too small to make strong recommendations and larger studies are needed to confirm the results. An additional limitation was the placement of PD stents with internal flanges, which might have prevented spontaneous dislodgment of the stents.

Guidewire entry to the PD was one of the high risk inclusion criteria in the current study. There are many instances where the guidewire is introduced to the PD unintentionally. Many experts do not manipulate the PD solely for placing prophylactic PD stents and limit PD stent insertion to patients with unintentional PD guidewire entry [20, 32–35]. Our results support this strategy of limiting PD stent insertion to cases where the guidewire has already entered the PD repeatedly, and the use of pharmacological prophylaxis in other high risk patients might be common among the indications for use of PD stents during ERCP.

To conclude, while the results of this study do not provide conclusive evidence regarding the additional benefit of PD stenting in patients receiving pharmacological prophylactic measures, the benefit (if any) is likely to be small. Moreover, although our findings showed inconclusive results regarding noninferiority of pharmacological prophylaxis in preventing PEP among high risk groups, larger trials are needed.

Acknowledgment

The study was funded by the Digestive Disease Research Institute of Tehran University of Medical Sciences. Special thanks to Professor Alan Barkun (McGill University) and Professor Robert Enns (MD, FRCP, St Paul’s Hospital, University of British Columbia) for their great help in improving the manuscript. We also thank Dr. Alireza Nateghi (Alborz Darou Pharmaceutical Company) for providing the study medications, and GI fellows, Research fellows Dr. Maryam Faezian, Dr. Hamideh Shahsavand-Einanolou, Dr. Hamideh Fakhrai, Dr. Roya Rahimi, and the nurses of Tehran Shariati Hospital for their help in conducting this study.
Competing interests

None

References


