Can topical epinephrine application to the papilla prevent pancreatitis after endoscopic retrograde cholangiopancreatography? Results from a double blind, multicentre, placebo controlled, randomised clinical trial

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ABSTRACT

Background and study aims Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a complication associated with important morbidity, occasional mortality and high costs. Preventive strategies are suboptimal as PEP continues to affect 4% to 9% of patients. Spraying epinephrine on the papilla may decrease oedema and prevent PEP. This study aimed to compare rectal indomethacin plus epinephrine (EI) versus rectal indomethacin plus sterile water (WI) for the prevention of PEP.

Patients and methods This multicentre randomised controlled trial included patients aged >18 years with an indication for ERCP and naive major papilla. All patients received 100 mg of rectal indomethacin and 10 mL of sterile water or a 1:10000 epinephrine dilution. Patients were asked about PEP symptoms via telephone 24 hours after the procedure. The trial was stopped half way through after a new publication reported an increased incidence of PEP among patients receiving epinephrine.

Results Of the 3602 patients deemed eligible, 3054 were excluded after screening. The remaining 548 patients were randomised to EI group (n=275) or WI group (n=273). The EI and WI groups had similar baseline characteristics. Patients in the EI group had a similar incidence of PEP to those in the WI group (3.6% (10/275) vs 5.12% (14/273), p=0.41). Pancreatic duct guidewire insertion was identified as a risk factor for PEP (OR 4.38, 95% CI (1.44 to 13.29), p=0.009).

Conclusion Spraying epinephrine on the papilla was no more effective than rectal indomethacin alone for the prevention of PEP.

Trial registration number This study was registered with ClinicalTrials.gov (NCT02959112).

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a routinely performed endoscopic procedure with multiple therapeutic applications, but it is not devoid of potential complications. The overall complication rate for ERCP is typically reported as 5% to 10%. Post-ERCP pancreatitis (PEP) is the most common and feared complication,
with a frequency and mortality of 3% to 9% and 3%, respectively.1,2 Risk factors for the development of PEP include those related to the patient and those associated with the procedure. Patient-related risk factors include female sex, previous pancreatitis, previous PEP, sphincter of Oddi dysfunction (SOD), jaundice, first ERCP and intraductal papillary mucinous neoplasm.3,4 Procedure-related factors include difficult cannulation, endoscopic sphincterotomy, precut sphincterotomy and injection into the main pancreatic duct (PD).3-5

Multiple strategies have been evaluated to reduce the risk of PEP, including aggressive fluid resuscitation, PD stenting, use of gabexate, ulinastatin, statins, secretin, antibiotics, rectal indomethacin and epinephrine sprayed on the papilla. The use of rectal indomethacin is supported by evidence,6-11 and is currently recommended by the European Society of Gastrointestinal Endoscopy and the American Society for Gastrointestinal Endoscopy.12 13 Regarding the use of epinephrine, one trial showed that epinephrine sprayed on the major papilla can reduce the risk of PEP,14 and a network meta-analysis suggested that the most efficacious agent to prevent PEP is topical epinephrine.15 It remains unclear whether the combination of rectal indomethacin and sprayed epinephrine has an added benefit, with a preliminary study showing a potential benefit over indomethacin alone,15 while a multicentre double-blind randomised trial reported no benefit in high-risk patients.16 Of particular concern, a recent multicentre randomised controlled trial was stopped early after an interim analysis concluded that the combination may actually be detrimental.17 Therefore, the aim of this study was to compare the efficacy and safety of rectal indomethacin plus epinephrine sprayed on the papilla (EI) versus rectal indomethacin and sterile water (WI) for the prevention of PEP, and to determine the risk factors associated with this complication.

PATIENTS AND METHODS

Study design

This multicentre randomised placebo-controlled trial was conducted in two hospitals. All patients provided written informed consent. This study received no commercial support.

Patients

We included patients aged 18 years or older with naive papilla and indication for ERCP. We excluded those patients with an allergy to indomethacin or epinephrine, pancreatic head cancer, chronic calcifying pancreatitis, renal insufficiency (serum creatinine >1.4 mg/dL), endotracheal intubation due to an indication other than ERCP, biliary-digestive bypass, pregnant patients and those unwilling to provide consent. Elimination criteria were the injection of epinephrine into the papilla to control bleeding and prophylactic placement of a pancreatic stent. Enrolment began in May 2016 and ended in June 2019. Recruitment was stopped early at 50% enrolment because during the enrolment of our patients, one published study had found no difference in the incidence of PEP with epinephrine irrigated in the papilla,16 and a different one even reported a higher incidence of this complication.17 We included patients with high and average risk for PEP.

Randomisation and masking

The study coordinator performed the block randomisation, enrolled participants, assigned participants to interventions and collected data during procedure. Participants were allocated into groups by block randomisation using computed-generated numbers, in which 24 blocks were created with 40 patients each. The two groups were EI versus WI. Patients, endoscopists, nurses and assistants who participated in the procedure were kept blinded to the group allocation. Investigators who participated in the evaluation of post-ERCP complications were also blinded to group allocation to ensure blinding.

Endoscopic retrograde cholangiopancreatography and treatment regimens

ERCP procedures were performed with a videoduedenoscope (TJF-180F; Olympus, Tokyo, Japan), using iobitrudol 300 mg/mL (Xenetix 300) as the contrast medium during the cholangiography. Patients were administered supplementary oxygen (3–5 L/min) via a nasal cannula or a nasal mask, and their vitals were monitored during the procedure. All patients received local anaesthesia with a lidocaine spray. Systemic analgesia and sedation with propofol, fentanyl and midazolam were administered by a certified anaesthesiologist. Based on comorbidities and respiratory and haemodynamic status, some patients were intubated before the procedure. All ERCPs were performed by one of six staff physicians, all of them with at least 5 years of experience with >200 ERCPs per year.

All patients were given a dose of rectal indomethacin (100 mg) at the beginning of the ERCP. Depending on the experimental group, either 10 mL of sterile water or 10 mL of a 1:10000 epinephrine dilution (0.1 mg/mL) was sprayed on the ampulla through a biliary balloon or a sphincterotome, avoiding any direct contact with the papilla during irrigation at the end of the procedure.

Outcomes, assessments and follow-up

The primary outcome of the study was to determine the incidence of PEP, and the secondary outcome was to identify the risk factors associated with the development of PEP.

Before the ERCP, relevant clinical information was collected, including age, gender, history of cholecystectomy, cholangitis or pancreatitis, diagnosis of SOD, intraductal papillary mucinous neoplasm, indication for ERCP and the presence of active cholangitis. Body mass index, triglyceride and bilirubin levels were recovered from each patient’s chart. During the procedure,
we recorded the common bile duct diameter, number of cannulation attempts, total volume of contrast media used, PD guidewire insertion, contrast injection of the PD, number of injections of the PD and the presence of choledocholithiasis or periampullary diverticulum. We also documented if any of the following procedures were performed: biliary and/or pancreatic sphincterotomy, precut sphincterotomy, balloon dilatation of the sphincter of Oddi, ampullectomy, brushing of the PD or placement of a naso-biliary catheter. The total length of the procedure was documented in minutes, comprising the time from introduction to withdrawal of the duodenoscope. Difficult cannulation was defined as being unable to cannulate after 5 min.

Patients were considered high risk for PEP if they met at least one major criteria (clinical suspicion of SOD, a history of PEP, pancreatic sphincterotomy, precut sphincterotomy, ≥8 cannulation attempts, pneumatic dilatation of an intact biliary sphincter or ampullectomy) or two or more of the minor criteria (women younger than 50 years, a history of recurrent pancreatitis ≥2 times, ≥3 injections of contrast into the PD with ≥1 injection to the tail of the pancreas, opacification of pancreatic acini or brush cytology performed on the PD).

After the procedure, patients were monitored in the recovery room for 2 hours and then discharged. Symptoms of acute pancreatitis or any other complication were interrogated at baseline while in the recovery room, and then by telephone 24 hours and 7 days after the procedure. Serum levels of pancreatic enzymes were determined only if the patient developed abdominal pain after ERCP. In those patients whose enzyme levels were normal despite a high suspicion of pancreatitis, a contrast-enhanced CT scan of the abdomen was performed to rule out the diagnosis. Patients with PEP or other complication associated with ERCP (eg, bleeding, cholangitis, perforation) received standard-of-care management for these complications. The end of follow-up was at hospital discharge in patients who developed PEP or any other complication associated with ERCP, or after 7 days in patients who had an uncomplicated course.

PEP was defined according to the following criteria: (1) new onset of upper abdominal pain; (2) elevation in serum amylase or lipase levels of at least three times...
the upper limit of the normal range at 24 hours after the procedure; and (3) hospitalisation or prolonged hospitalisation for at least 2 days. The severity of PEP was based on Cotton’s criteria: (1) mild pancreatitis, if cases required fewer than 3 days of hospital admission; (2) moderate pancreatitis, if patients required from 4 to 10 days of admission; and (3) severe pancreatitis, if patients required more than 10 days of hospitalisation and/or it was complicated by the development of pancreatic necrosis or a pseudocyst.

After the publication of Luo et al who reported an increased incidence of PEP in patients receiving epinephrine and the publication of Kamal et al who did not find differences between high risk groups, we decided to stop the trial in conjunction with The Committee of Investigation and The Committee of Ethics in Investigation of our hospital.

**Statistical analysis**

We used the formula for two proportions of two independent groups and estimated that 948 patients (474 in each arm) would be needed to detect a difference of 5% to 10% in the risk of PEP with a power of 80% and a two-tailed alpha of 5%. Numerical variables are presented as the mean and SD, and categorical variables as the absolute and relative frequencies, excluding observations from the denominator when missing. The Student’s t-test and χ² test were used to compare continuous and categorical variables between groups, respectively. Variables with p<0.2 probability of having an association with PEP in the univariable analysis were included in the multivariable analysis, we use a stepwise backward approach. Logistic regression was used, with a p value of ≤0.05 considered statistically significant. All results are from intention-to-treat analysis. Data analysis was performed with SPSS Statistics 24.0 (Chicago, Illinois, USA).

**RESULTS**

During the study period, 3602 patients were deemed eligible, but 3054 were excluded after screening (2976 did not meet the inclusion criteria, 78 met the exclusion criteria; figure 1). The remaining 548 patients were randomly assigned to the EI group (n=275) or the WI group (n=273). The EI and WI groups had similar baseline characteristics (table 1).

The overall cannulation success rate for patients was 98.5%. The ERCP procedure-related parameters and risk factors for PEP in the EI and WI groups were comparable, except for trainee involvement, trainees were involved in 95.8% of the procedures, 258 (93.8%) in the EI group and 267 (97.8%) in the WI group (p=0.020) (table 2). A total of 325 (59.3%) patients were considered at high risk for PEP, 154 (56%) in the EI group and 171 (62.6%) in the WI group (p=0.125). The two most common risk factors for PEP were choledocholithiasis (59%) and malignant biliary strictures (11%).

| Table 1 | Distribution of baseline characteristics of included patients by group |
|---------|--------------------------|
| **EI (n=275)** | **WI (n=273)** | **P value** |
| Age, years (mean±SD) | 50.3±21.4 | 51.8±20.3 | 0.409 |
| Female, n (%) | 188 (68.3) | 192 (70.3) | 0.617 |
| Prior history of cholecystectomy, n (%) | 99 (36) | 101 (36.9) | 0.808 |
| Current cholangitis, n (%) | 41 (14.9) | 27 (9.8) | 0.074 |
| History of cholangitis, n (%) | 11 (4) | 12 (4.3) | 0.817 |
| Current pancreatitis, n (%) | 1 (0.3) | 4 (1.4) | 0.175 |
| History of pancreatitis, n (%) | 23 (8.3) | 27 (9.8) | 0.534 |
| Diabetes mellitus, n (%) | 53 (19.2) | 44 (16.1) | 0.333 |
| Total bilirubin, mg/dL (mean±SD) | 5.1±5.1 | 4.9±5.5 | 0.645 |
| Direct bilirubin, mg/dL (mean±SD) | 3.8±4.1 | 3.6±4.1 | 0.460 |
| Body mass index, kg/m² (mean±SD) | 24.6±9.2 | 25±7.8 | 0.589 |
| Triglycerides, mg/dL (mean±SD) | 162.4±85.6 | 158.9±51.3 | 0.798 |
| **Indications** | | | |
| Choledocholithiasis, n (%) | 208 (75.6) | 202 (73.9) | 0.657 |
| Bile leak, n (%) | 21 (7.6) | 19 (6.9) | 0.760 |
| Malignant biliary stricture, n (%) | 8 (2.9) | 9 (3.2) | 0.793 |
| Benign or undetermined biliary stricture, n (%) | 7 (2.5) | 16 (5.8) | 0.052 |
| Benign pancreatic diseases, n (%) | 6 (2.1) | 7 (2.5) | 0.768 |
| Suspected SOD, n (%) | 1 (0.3) | 0 | – |
| Other, n (%) | 24 (8.7) | 21 (7.6) | 0.659 |

Student’s t-test and χ² test were used.
EI, epinephrine and rectal indomethacin; SOD, sphincter of Oddi dysfunction; WI, sterile water and rectal indomethacin.
Factors were precut sphincterotomy (197 patients, 35.9%) and difficult cannulation (173 patients, 31.6%).

PD guidewire manipulation occurred in 21% of the EI group and 26% of the WI group and pancreatography in 4.7% and 5.8%, respectively. It was intentional in 13 patients because of pancreatic diseases, 129 patients had PD guidewire insertion, 59 of them one time, 35 two times, 15 three times and 20 four or more times. A double wire technique to achieve cannulation was done in 10 patients. PD therapeutic stents were placed in 13 patients and prophylactic stents were placed in also 13 patients, in the remaining cases a PD stent was not placed because loss of access to the PD during procedure or endoscopist decision.

There were no significant differences between the groups for complications and their severity (Table 3). The overall incidence of PEP was 4.3%. Patients in the EI group had a similar incidence of PEP to those in the WI group (3.6% (10/275) vs 5.1% (14/273), p=0.414). According to Cotton's criteria, mild, moderate and severe PEP were comparable between the two groups. Severe PEP was only found in one patient in the EI group. The overall mortality was 1.4%, with five deaths due to a malignant tumour.
the use of rectal indomethacin. Other options have also been studied, including pancreatic stent, vigorous hydration and epinephrine sprayed on the major papilla. In the past, two studies were conducted with sprayed epinephrine on the papilla for prevention of PEP, the first was conducted by Matsushita et al in 2009, they

### Table 3 Complications observed in the included patients by group

|                           | EI (n = 275) | WI (n = 273) | P value |
|---------------------------|--------------|--------------|---------|
| Total complications       | 40           | 41           | 0.876   |
| Pancreatitis              | 10           | 14           | 0.393   |
| Mild                      | 8            | 9            | 0.793   |
| Moderate                  | 1            | 5            | 0.214   |
| Severe                    | 1            | 0            | -       |
| Abdominal pain with normal lipase | 9            | 5            | 0.285   |
| Bleeding                  | 9            | 3            | 0.147   |
| Mild                      | 5            | 3            | 0.729   |
| Moderate                  | 3            | 0            | -       |
| Severe                    | 1            | 0            | -       |
| Cholangitis               | 5            | 10           | 0.185   |
| Mild                      | 2            | 1            | 0.994   |
| Moderate                  | 2            | 8            | 0.107   |
| Severe                    | 1            | 1            | 0.481   |
| Cholecystitis             | 1            | 3            | 0.61    |
| Fever                     | 4            | 0            | -       |
| Death related to ERCP     | 1            | 2            | 0.994   |
| Death related to malignant tumour | 1            | 4            | 0.364   |
| Pancreatitis by group of risk |             |              |         |
| Pancreatitis in high risk patients, n (%) | 8/154 (5.1) | 12/171 (7.0) | 0.52    |
| Pancreatitis in average risk patients n (%) | 2/121 (1.6) | 2/102 (1.9)  | 0.865   |

χ² test was used.

EI, epinephrine and rectal indomethacin; ERCP, endoscopic retrograde cholangiopancreatography; WI, sterile water and rectal indomethacin.

### Table 4 Univariable and multivariable analysis of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis in the included patients, logistic regression analysis

| Univariable analysis                   | B   | SE  | Wald χ² | OR (95% CI) | P value |
|----------------------------------------|-----|-----|---------|-------------|---------|
| Female                                 | −1.169 | 0.624 | 3.503 | 0.31 (0.91 to 1.05) | 0.061 |
| Prior cholecystectomy                  | 0.934 | 0.424 | 4.850 | 2.54 (1.10 to 5.84) | 0.028 |
| History of pancreatitis                | 1.291 | 0.497 | 6.747 | 3.63 (1.37 to 9.63) | 0.009 |
| Difficult cannulation                  | 1.167 | 0.425 | 7.553 | 3.12 (1.39 to 7.39) | 0.006 |
| Volume of contrast media               | −0.060 | 0.021 | 8.021 | 0.94 (0.90 to 0.98) | 0.005 |
| Biliary sphincterotomy                 | −0.826 | 0.435 | 3.604 | 0.43 (0.18 to 1.02) | 0.058 |
| Pancreatic sphincterotomy              | 2.359 | 0.535 | 19.415 | 10.58 (3.70 to 30.22) | <0.001 |
| Pancreatic duct guidewire insertion    | 2.190 | 0.462 | 22.510 | 8.93 (3.61 to 22.07) | <0.001 |
| Pancreatography                        | 2.240 | 0.499 | 20.145 | 9.39 (3.53 to 24.99) | <0.001 |
| Number of cannulation attempts by professor | 0.153 | 0.044 | 11.983 | 1.16 (1.06 to 1.27) | 0.001 |
| Time of cannulation attempts by professor | 0.076 | 0.032 | 5.483 | 1.07 (1.01 to 1.15) | 0.019 |
| High risk patients                     | 1.278 | 0.555 | 5.307 | 3.59 (1.21 to 10.65) | 0.021 |

| Multivariable analysis                 |       |     |         |             |         |
|----------------------------------------|-------|-----|---------|-------------|---------|
| Prior cholecystectomy                  | 0.926 | 0.437 | 4.48    | 2.52 (1.07 to 5.94) | 0.034 |
| Pancreatic duct guidewire insertion    | 2.186 | 0.464 | 22.19   | 4.38 (1.44 to 13.29) | <0.001 |
included 185 patients in the epinephrine group and 185 in the saline solution group, they found a decrease in the number of cases of PEP, 0/185 cases in the epinephrine group and 4/185 cases in the saline solution group, however the p value was 0.12, its sample size was questioned. The other study was conducted by Xu et al in 2011, they included 461 patients in the epinephrine group and 480 in the saline solution group, they found a decrease in the number of cases of PEP, 9/461 cases in the epinephrine group and 31/480 cases in the saline solution group, p value was 0.008. It should be noted that in both studies the ERCPs were only diagnostic, cannulation times were prolonged, there was not a standardisation definition of PEP and rectal indomethacin was not used. When these results were included in the previously mentioned network meta-analysis, epinephrine sprayed into the papilla was effective in reducing the incidence of PEP (OR 0.25; 95% CI 0.06 to 0.65; Number Needed to treat (NNT) 15).

Our results are consistent with those of other studies that have explored the use of epinephrine in conjunction with rectal indomethacin. A randomised trial by Kamal et al in patients at high risk of PEP found an incidence of 6.4% (31/482) in the indomethacin-only group versus 6.7% (32/477) in the combination group (p=0.87). Even though the PEP incidence was double that reported in the current study, likely because the study by Kamal et al was focussed on high-risk patients, the results point toward no added benefit of epinephrine in combination with indomethacin. While our study suggests that there is no added benefit of epinephrine, our findings do not suggest that it is detrimental to patients. This is in contrast to the findings of a multicentre double-blind trial performed by Luo and colleagues, in which 1158 patients were randomised to either indomethacin-only or indomethacin plus sprayed epinephrine groups, which found an increased incidence of PEP in the combination group (5.3% vs 8.5%, p=0.03). The authors concluded that sprayed epinephrine should not be used in combination with rectal indomethacin for the prevention of PEP because of the potential for increasing the incidence of PEP. We believe that this discordance could, at least in part, be due to the lower epinephrine concentration (0.01%) used in the current study compared with that used by Kamal et al and Luo et al (0.02%). It is possible that the vasoconstriction effect of epinephrine could reduce the bioavailability of indomethacin in the papilla area, precluding it from achieving a satisfactory result. Therefore, using a higher dose would probably accentuate this effect. Supporting this theory, Hatami and colleagues investigated the effect of epinephrine alone on PEP, in which 66 cases were randomised to the epinephrine-alone group, 68 individuals to the indomethacin group and 58 patients to the combination group. The overall incidence of PEP in this study was 3.6% (7/192), with six cases in the indomethacin group, one in the epinephrine group and no cases in the combination group; however, the small size of this study limits its conclusions.

With our results, we cannot conclude that spraying epinephrine is harmful, but it does not appear to be useful, results that are accordant with the conclusion of a recently published systematic review and meta-analysis which included the studies of Hatami, Luo and Kamal et al. The reason behind this lack of effectiveness may be as Kamal and colleagues suggest, that epinephrine reduces the concentration of indomethacin, or, even worse, that epinephrine antagonises the effect of indomethacin. A third reason could be that epinephrine is not as good as indomethacin at preventing PEP, and that any benefit that it may confer is obscured by indomethacin. In order to sustain the last hypothesis, a non-inferiority trial would need to be conducted for epinephrine and indomethacin, although this will probably never happen due to ethical concerns. A fourth possible reason for the limited efficacy of epinephrine could be that, once it is sprayed, it has a short and limited time of action, which is insufficient to facilitate the flow of pancreatic juices in the mid-term.

One of the limitations of our study is that we had to stop enrolment earlier than planned, so our study may not have had enough power to detect superiority, as stipulated based on the sample size calculation, also the negative effects of the intervention could have been missed. However, based on our preliminary results, together with the findings of Kamal et al and Luo et al, we consider that it would have been unethical to continue with the study. Other important limitation is that patients were not randomised by level of risk for PEP. Another potential limitation is that we could not control the aggressiveness of hydration that patients received, which might have influenced the results, but is not a common practice in our hospital to give 3 L of intravenous fluid during ERCP. However, due to randomisation and masking, it is most probably the case that hydration aggressiveness ended up being equally distributed between the groups, also the high and low risk patients. A lot of our patients had a prior sphincterotomy because our institution is a high volume tertiary hospital and most of the cases evaluated are complicated and had previous ERCP, which could compromise the external validity and could affected some results, like PEP incidence. Our study also has several strengths. First, this study represents the first data from a Latin-American population. Second, the study was designed as a multicentre study with blinding of all significant physicians (doctors who performed the ERCP and those who evaluated the outcomes). Finally, we included patients with different levels of risk for PEP, making our results more applicable in clinical practice.

In conclusion, the addition of epinephrine sprayed on the papilla was no more effective than rectal indomethacin.
alone for the prevention of PEP, but it did not increase the risk of any other complication.

Acknowledgements To CONACYT (CVU 429684).

Contributors AFR-M, CM-V and FI. T-Á: conception and design; AFR-M, VJB-B and FL-T: A: analysis and interpretation of the data; AFR-M and FI. T-Á: critical revision of the article; AFR-M and FI. T-Á: drafting of the article; AFR-M and FI. T-Á: critical revision of the article for important intellectual content; JGG-C, LFG-C, JR-G, LU-D, JAO-R, JFT-C, GV-A, Dk-R, GG-F, MAR-L, FV-A and LZ-N: collected data; FIT-A, AFR-M, CM-V, JGG-C, LFG-C, JR-G, LU-D, JAO-R, JFT-C, GV-A, Dk-R, GG-F, MAR-L, FV-A and LZ-N: final approval of the article.

Funding National Council of Science and Technology (CONACYT) doctoral scholarship.

Disclaimer The study sponsors had no role in the study design, collection, analysis, interpretation of data, writing of the report nor the decision to submit the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by institutional review boards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be available upon request to the correspondence author. Dr Félix Téllez-Avila: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán/Vasco de Quiroga #15, Sección XlII Tlalpan, Zip Code 14000, Mexico City, México. Email: felix.telleza@gmail.com.

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