# Somatostatin for prevention of post-ERCP pancreatitis: a randomized, double-blind trial

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**Background and study aims:** Meta-analyses suggest that an intravenous bolus or a high dose continuous infusion of somatostatin reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). Clinical guidelines, however, do not recommend this prophylaxis. The aim of this randomized, double-blind clinical trial was to evaluate the effect of somatostatin on the incidence of post-ERCP pancreatitis.

**Patients and methods:** Patients undergoing ERCP at a single center were randomized to either intravenous bolus of somatostatin followed by a short (4-hour) continuous infusion, or to a similar placebo regimen. The primary outcome was post-ERCP pancreatitis, defined as abdominal pain with an amylase level at least three times higher than the upper limit of normality 24 hours after the ERCP and requiring admission for at least 2 days.

**Results:** A total of 510 patients were enrolled (255 patients per group) and all completed follow-up. The main indications for ERCP were choledocholithiasis (62 %), and biliary malignant stricture (31 %). Post-ERCP pancreatitis occurred in 19 patients (7.5 %) in the somatostatin group and 17 patients (6.7 %) in the placebo group (relative risk [RR] 1.12, 95 % confidence interval [95 %CI] 0.59 – 2.1; $P$ = 0.73). The number of cases of moderate or severe acute pancreatitis was similar in the somatostatin (2.4 %) and the placebo (3.5 %) groups (RR 0.67, 95 %CI 0.24 – 1.85, $P$ = 0.43). No side effects were observed related to the use of somatostatin.

**Conclusions:** Administration of an intravenous bolus of somatostatin followed by a short continuous infusion does not reduce the incidence of post-ERCP pancreatitis.

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## Introduction

Most cases of post-ERCP pancreatitis are mild or moderate, but up to 10 % of cases may be severe, and potentially fatal [1]. Several strategies have been postulated to diminish the risk of this complication, the most common being the administration of different drugs [1 – 3]. One of these drugs, somatostatin, acts through several mechanisms: it minimizes pancreatic secretion [4 – 5] and reduces pressure of the sphincter of Oddi [6 – 7], thereby decreasing intrapancreatic pressure; it modulates cytokine activity [8]; and induces apoptosis of pancreatic acinar cells [9]. These mechanisms might protect against post-ERCP pancreatitis. In view of these effects, somatostatin has been widely studied in randomized controlled trials [10 – 14] and in several meta-analyses [15 – 18]. However, the results are controversial, and although some of these studies have described a reduction in this complication, the drug has not been recommended in ERCP guidelines [1 – 3]. Possible explanations are that the impact of somatostatin might not be clinically relevant and that trials differed with regard to administration regimen. The two more recent meta-analyses suggested that a somatostatin bolus or a long infusion (more than 12 hours) can reduce the risk of pancreatitis, while a short infusion (less than 6 hours) does not [17 – 18]. However, most ERCPs are performed on an outpatient basis and a long infusion requires overnight hospitalization.

We hypothesized that an intravenous bolus injection of somatostatin followed by a short (4-hour) continuous infusion might enforce the effect of a bolus alone in preventing post-ERCP pancreatitis.

## Patients and methods

### Study design

We conducted a single-center, randomized, placebo-controlled, and double-blind clinical trial to evaluate the effect on the incidence of post-ERCP pancreatitis of an intravenous bolus of somatostatin followed by a short (4-hour) continuous infusion. All patients aged 18 or older who underwent an ERCP were screened for inclusion. Exclusion criteria were: documented intolerance to somatostatin, acute pancreatitis at the time of endoscopy, acute coronary syndrome in the 6 months preceding the ERCP, any medical condition in which somatostatin was otherwise contraindicated or indicated, and pregnancy or breastfeeding. Patients with previous sphincterotomy or chronic pancreatitis were also excluded because of their low risk of post-ERCP pancreatitis. The study protocol was approved by the local ethics committee. All eligible patients received oral and written information about the study and gave their written consent prior to inclusion.

Data were prospectively collected in a standardized data form, with information gathered on patient demographics, endoscopic procedure features, possible adverse effects of medication, complications, and follow-up. Allocation was predetermined using a computer-generated random list prepared by the pharmacology staff, without block randomization or stratification. Nobody else had access to this list until the end of the study period. In the pharmacology department, somatostatin and placebo were masked daily, and sequentially numbered according to the random list. Patients were sequentially included according to medication received. Patients, study investigators, clinical staff in charge of patients, and data collectors were all blinded to the allocation until the study database was complete. Data were analyzed by the principal investigators, who were not blinded for the study intervention at this point.

The somatostatin group received an intravenous bolus of 250 µg of somatostatin (EFG; Combino Pharm) slowly infused over 3 minutes prior to the attempt at cannulation of the papilla of Vater. This was immediately followed by a 4-hour continuous infusion of the drug at 250 µg/h. The total dose of somatostatin was thus 1250 µg. The placebo group received the equivalent volume of saline solution both as an initial bolus and as a continuous infusion. Somatostatin or placebo were administered by the study investigators.

All the procedures were performed by experienced medical endoscopists in the gastroenterology department at a tertiary institution. All endoscopies were performed with patients under propofol sedation controlled by the endoscopist, usually with an initial infusion of 1 – 2 mg of midazolam. The guidewire cannulation method was used in all cases.

After the procedure, patients were closely observed for a minimum of 6 hours. Blood samples were collected before and 4 hours after the procedure. Analyses included serum amylase and lipase levels. Outpatients were evaluated at the day care hospital by the gastroenterology staff, who were blinded for the study group, and were discharged at 6 hours if no symptoms or signs of complication were observed. In accordance with routine practice, those with a suspected complication were admitted to the gastroenterology department. In these cases, blood testing and/or a computed tomography (CT) scan were performed according to the hospital protocols. For hospitalized patients, additional samples were collected 24 hours after the procedure only if acute pancreatitis was suspected. At 7 days after the procedure, discharged patients were contacted by telephone to evaluate their post-procedure course. Participants with confirmed complications were followed until resolution.

### Outcomes and definitions

#### Primary outcome

The main outcome of the study was post-ERCP pancreatitis, defined according to the criteria established by Cotton et al.: abdominal pain with amylase level at least three times the upper limit of normality 24 hours after the ERCP, and requiring admission or prolongation of planned admission to at least 2 days [19].

#### Secondary outcomes

These were as follows:

- Severity of post-ERCP pancreatitis. Pancreatitis was graded as "mild" when hospitalization was required for 2 – 3 days, "moderate" when hospitalization was required for 4 to 10 days, and "severe" when hospitalization was prolonged more than 10 days, when there were necrohemorrhagic features or pseudocysts, or when endoscopic, percutaneous, or surgical intervention was required [19].
- Asymptomatic hyperamylasemia, defined as an increase of serum amylase concentrations by at least threefold the upper limit of normality, without symptoms of pancreatitis. This was evaluated at 4 hours for outpatients and those inpatients who did not require subsequent blood tests. For other inpatients, it was evaluated in any blood test during the first 24 hours.
- Other ERCP complications (e.g. perforation, bleeding, cholangitis) as defined by Cotton et al. [19].
- Safety of somatostatin administration. Possible adverse events were specifically collected in all patients on the standardized data form during procedure and follow-up.

To further evaluate the influence of somatostatin on the incidence of pancreatitis in patients defined as high risk, we performed a secondary analysis of complications including only patients with an increased risk of post-ERCP pancreatitis. This increased risk was defined in patients with one or more of the following major criteria: clinical suspicion of sphincter of Oddi dysfunction, history of post-ERCP pancreatitis, pancreatic sphincterotomy, precut sphincterotomy, more than eight cannulation attempts, pneumatic dilation of an intact biliary sphincter, or ampullectomy [20]. This group also included patients with two or more of the following minor criteria: female and younger than 50 years; history of recurrent pancreatitis with two or more episodes; three or more injections of contrast into the pancreatic duct; opacification of pancreatic acini, or acquisition of a cytological specimen from the pancreatic duct. This analysis was not defined a priori in the study protocol as these exact criteria had not been defined when our study was designed.

### Sample size calculation

According to previous literature [1 – 3] and unpublished pilot data from clinical audits in our institution, we assumed an incidence of acute pancreatitis of 7.7 % in the control group, and we expected a reduction to 2.5 % in the study group (relative reduction of 67.5 %). Therefore, using a two-tailed test and with alpha and beta values of 0.05 and 0.2, we estimated that 255 patients would be required per group.

### Statistical analysis

Continuous variables were described using mean (standard deviation [SD]) when normally distributed and as median (interquartile range [IQR]) when skewed. Proportions were used for ca-

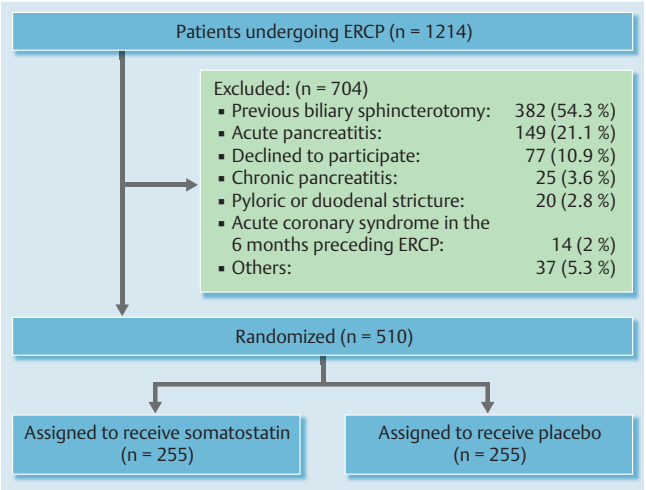


**Fig. 1** Somatostatin for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP): trial flowchart.

tegorical variables. The chi-squared test was used to analyze the efficacy of the study intervention on reducing post-ERCP pancreatitis (primary outcome). Similarly, the chi-squared test was also used to investigate the effect of somatostatin infusion (as described above) on pre-specified secondary outcomes.

Potential risk factors of post-ERCP pancreatitis were defined a priori, based on previous literature. Predictors that in cross-tabs had a value of 0 patients in any of the cells were excluded. Multivariate logistic regression models were fitted to assess the association between baseline characteristics and risk of post-ERCP pancreatitis. Predictors for the multivariate analysis were based on the ESGE guideline definite risk factors (sphincter of Oddi dysfunction, previous pancreatitis, female gender, precut sphincterotomy, and pancreatic injection) [1], and on significant factors of the univariate analysis. A maximum number of four predictors was allowed in the final model to prevent overfitting. Predictors with no patients affected by the risk factor of interest and/or the study outcome were excluded. Backwards stepwise methods were used to identify key risk factors amongst the remaining ones. Univariate and multivariate adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) are reported. All statistical analyses were performed using the SPSS Statistical Package (version 19.0; SPSS Inc., Chicago, Illinois, USA).

## Results

### Patients and groups

From May 2009 to February 2013, a total of 1214 participants undergoing ERCP procedures were eligible for assessment for the study. Of these, 704 were excluded as detailed in the flowchart (**Fig. 1**). Finally, 255 patients were randomized to each intervention. Participants' demographic and baseline characteristics were similar for the two groups (**Table 1**). The main indications for ERCP were choledocholithiasis (62%) and biliary malignant stricture (31%). Nearly half of the procedures were performed on an outpatient basis (45.5%). The characteristics of the ERCP procedure were also similar for the two groups (**Table 2**). The 33 cases with failed cannulation were included in the difficult cannulation group. All patients completed the follow-up.

### ERCP complications

The primary analysis was intention-to-treat and involved all patients who were randomly assigned.

Complications occurred in 73 of 510 procedures (14.3%). Acute pancreatitis was the most common complication, with a total of 36 episodes (7.1%), of which 21 (58%) were mild, 13 (36%) were moderate, and 2 (6%) were severe. Bleeding was observed in 21 cases (4.1%): 9 required endoscopic treatment and 1 cirrhotic patient required angiographic therapy. Additionally, 15 of these patients required blood transfusion. Perforation occurred in three patients (0.6%). Two of the three required surgery: this was because of duodenal dilation in the context of a neoplastic infiltration in one patient and a difficult multiple choledocholithiasis extraction in the second. The third perforation occurred during a precut maneuver and was managed conservatively with clips and antibiotics. There were 12 episodes of cholangitis (2.4%), all managed conservatively with antibiotics. One patient died 24 hours after the ERCP because of an acute pulmonary edema. No side effects or complications related to the use of somatostatin were observed. Complications in each group were similar and are detailed in **Table 3**.

Acute pancreatitis occurred in 19 of 255 (7.5%) patients in the somatostatin group and in 17 of 255 (6.7%) patients in the placebo group (relative risk [RR] 1.12, 95%CI 0.59–2.1; $P$=0.73). The number of moderate and severe acute pancreatitis cases was similar in both groups: 6 (2.4%) patients in the somatostatin group and 9 (3.5%) patients in the placebo group (RR 0.67, 95% CI 0.24–1.85; $P$=0.43). One patient in each group had a severe acute pancreatitis, one of whom required drainage of an infected pseudocyst. No differences were observed when the 278 inpati-

**Table 1** Somatostatin for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP): demographic and baseline characteristics of study patients.

| | All patients n=510 | Somatostatin group n=255 | Placebo group n=255 | *P* value |
|---|---|---|---|---|
| Age, mean (SD), years | 73 (13) | 73 (14) | 73 (13) | 0.43 |
| Gender, n (%) | | | | 0.43 |
| Male | 241 (47.3%) | 116 (45.5%) | 125 (49%) | |
| Female | 269 (52.7%) | 139 (54.5%) | 130 (51%) | |
| Previous acute pancreatitis, n (%) | 80 (15.7%) | 36 (11.1%) | 44 (17.6%) | 0.33 |
| Pancreas divisum, n (%) | 4 (0.8%) | 1 (0.4%) | 3 (1.2%) | 0.62 |
| In- or outpatient, n (%) | | | | 0.86 |
| Inpatient | 278 (54.5%) | 140 (54.9%) | 138 (54.1%) | |
| Outpatient | 232 (45.5%) | 115 (45.1%) | 117 (45.9%) | |
| Bilirubin, mean (SD), µmol/L | 87 (129) | 93 (135) | 82 (122) | 0.35 |
| Amylase, mean (SD), U/L | 64 (43) | 65 (49) | 63 (36) | 0.65 |
| Lipase, mean (SD), (U/L) | 49 (61) | 49 (60) | 49 (62) | 0.95 |

SD, standard deviation

| | Somatostatin group n = 255 | Placebo group n = 255 | *P* value |
|---|---|---|---|
| Indication, n (%) | | | 0.88 |
| Choledocolithiasis | 160 (62.7 %) | 157 (61.6 %) | |
| Malignant stricture | 80 (31.4 %) | 78 (30.6 %) | |
| Previous acute pancreatitis | 9 (3.5 %) | 11 (4.3 %) | |
| Sphincter of Oddi dysfunction | 1 (0.4 %) | 3 (1.2 %) | |
| Others | 6 (2.4 %) | 9 (3.5 %) | |
| Cholangiography, n (%) | 239 (93.7 %) | 242 (94.9 %) | 0.57 |
| Biliary duct diameter, mean (SD), mm | 11 (4) | 11 (4) | 0.71 |
| Wirsung opacification, n (%) | 64 (25.1 %) | 69 (27.1 %) | 0.61 |
| Pancreatic acinarization, n (%) | 3 (1.2 %) | 9 (3.5 %) | 0.08 |
| Contrast injection, mean (SD), ml | 13 (8) | 14 (8) | 0.58 |
| > 3 pancreatic duct injections, n (%) | 20 (7.8 %) | 19 (7.5 %) | 0.87 |
| Biliary sphincterotomy, n (%) | 232 (91 %) | 233 (91.4 %) | 0.88 |
| Biliary stent | 54 (21.2 %) | 61 (23.9 %) | 0.46 |
| Precut sphincterotomy | 43 (16.9 %) | 35 (13.7 %) | 0.33 |
| Cannulation difficulty, n (%) | | | 0.27 |
| 1 – 5 attempts | 151 (59.2 % | 159 (62.4 %) | |
| 6 – 15 attempts | 53 (20.8 %) | 58 (22.7 %) | |
| > 15 attempts) | 51 (20 %) | 38 (14.9 %) | |
| Cannulation failure at first endoscopy, n (%) | 18 (7.1 %) | 15 (5.9 %) | 0.59 |
| Intradiverticular papilla, n (%) | 49 (19.2 %) | 37 (14.5 %) | 0.16 |
| Procedure duration, mean (SD), minutes | 31 (19) | 30 (22) | 0.57 |

SD, standard deviation

**Table 2** Procedure characteristics in trial of somatostatin for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP).

**Table 3** Complications in trial of somatostatin for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP).

| | Somatostatin n = 255 | Placebo n = 255 | *P* value |
|---|---|---|---|
| *Complications*, n (%) | | | |
| Acute pancreatitis | 19 (7.5 %) | 17 (6.7 %) | 0.73 |
| Bleeding | 9 (3.5 %) | 12 (4.7 %) | 0.5 |
| Cholangitis | 6 (2.4 %) | 6 (2.4 %) | 1 |
| Perforation | 2 (0.8 %) | 1 (0.4 %) | 0.62 |
| Death | 0 | 1 (0.4 %) | 1 |

ents were analyzed alone: acute pancreatitis occurred in 8/138 (5.8 %) patients in the placebo group, compared with 11/140 (7.9 %) patients in the somatostatin group (RR 1.36, 95 %CI 0.56 – 3.27). No differences were observed between the groups when they were compared for post-ERCP abdominal pain and asymptomatic hyperamylasemia. Abdominal pain occurred in 93 (36.5 %) patients in the somatostatin group and 75 (29.4 %) patients in the placebo group ($P$=0.11). Asymptomatic hyperamylasemia was observed in 33 (12.9 %) and 24 (9.4 %) patients respectively ($P$= 0.21).

The secondary analysis of complications in a subgroup of patients with increased risk of post-ERCP pancreatitis, as described in the methods section, included 210 patients, with 110 in the somatostatin group and 100 in the placebo group. The incidence of acute pancreatitis was 8.6 % (18 cases), without significant differences between the somatostatin group (8.2 %) and the placebo group (9 %) (RR 0.91, 95 %CI, 0.38 – 2.2).

## Post-ERCP pancreatitis risk factors

Univariate and multivariate predictors for post-ERCP pancreatitis are detailed in **Table 4**. Younger age was the only statistically associated risk factor both in the univariate and multivariate analysis.

## Discussion

The main finding in this randomized, placebo-controlled, double-blind clinical trial is that an intravenous bolus injection of somatostatin followed by a short (4-hour) continuous infusion did not influence the incidence of post-ERCP pancreatitis.

Studies in the literature to date are controversial. Initial prospective studies [10, 11] and an initial meta-analysis [15] suggested somatostatin could be useful in preventing post-ERCP pancreatitis. This meta-analysis included 10 studies with a total of 646 patients and showed that this complication decreased from 13.5 % to 5.6 %. However, most of the studies had a small number of patients – only one [11] recruited more than 100 participants – and the meta-analysis showed a low precision rate. Additionally, the possible role of the type of treatment regimen was not evaluated. In the last 12 years, nine high quality, prospective, randomized clinical trials have evaluated the effect of different treatment regimens for ERCP-related pancreatitis. These trials included 2758 patients and reported contradictory results. A second meta-analysis that included all these trials [16] concluded that a continuous infusion of somatostatin (either in a short regime of less than 6 hours or in a long regime of more than 12 hours) did not reduce acute pancreatitis. In fact, the incidence of acute pancreatitis increased slightly. The authors observed, however, that acute pancreatitis decreased from 11.3 % to 3 % after administration of a single bolus of somatostatin. This could be consistent with the pathogenic hypothesis which argues that the inflammatory response appears immediately after the endoscopic procedure. In the same year, a third meta-analysis [17] including 2256 patients, recruited only from randomized, placebo-controlled, double-blind studies, showed a 75.8 % decrease in the risk of pancreatitis when a somatostatin bolus was used, and also a 73.7 % decrease when long continuous infusion (more than 12 hours) was used. The authors hypothesized that a continuous infusion was only beneficial when more than 750 µg of somatostatin were administered. The most recent meta-analysis [18], including 10 studies and 2642 patients, also described a benefit of somatostatin, both

**Table 4** Univariate and multivariate analysis of risk factors associated with acute pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP).

| | Patients with pancreatitis n = 36 | Patients without pancreatitis n = 474 | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | Odds ratio (95 %CI) | *P* value | Odds ratio (95 %CI) | *P* value |
| Younger age, mean (SD), years | 68 (15) | 73 (13) | **1.03 (1.003 – 1.05)** | **0.03** | **1.03 (1.004 – 1.05)** | **0.02** |
| Female gender, n (%) | 21 (58.3 %) | 248 (52.3 %) | 1.28 (0.64 – 2.54) | 0.49 | 1.39 (0.69 – 2.79) | 0.35 |
| Previous acute pancreatitis, n (%) | 8 (22.2 %) | 72 (15.2 %) | 1.6 (0.7 – 3.64) | 0.26 | 1.55 (0.67 – 3.59) | 0.31 |
| Biliary duct diameter, mean (SD), mm | 11 (5) | 11 (4) | 0.97 (0.89 – 1.05) | 0.45 | | |
| Wirsung opacification, n (%) | 12 (33.3 %) | 121 (25.5 %) | 1.46 (0.71 – 3.01) | 0.3 | 1.62 (0.77 – 3.38) | 0.2 |
| Pancreatic acinarization, n (%) | 2 (5.6 %) | 10 (2.1 %) | 2.73 (0.58 – 12.96) | 0.21 | | |
| > 3 pancreatic duct injections, n (%) | 4 (11.1 %) | 35 (7.4 %) | 1.57 (0.53 – 4.69) | 0.34 | | |
| Precut sphincterotomy, n (%) | 5 (13.9 %) | 73 (15.4 %) | 0.89 (0.33 – 2.35) | 0.81 | | |
| Cannulation difficulty, n (%) | | | 1.24 (0.82 – 1.88) | 0.33 | | |
| 1 – 5 attempts | 18 (50 %) | 292 (61.6 %) | | | | |
| 6 – 15 attempts | 11 (30.6 %) | 100 (21.1 %) | | | | |
| > 15 attempts | 7 (19.4 %) | 82 (17.3 %) | | | | |
| Cannulation failure, n (%) | 1 (2.8 %) | 32 (6.8 %) | 0.4 (0.05 – 2.98) | 0.5 | | |
| ERCP duration, mean (SD), minutes | 31 (17) | 30 (21) | 1 (0.98 – 1.02) | 0.94 | | |
| Intradiverticular papilla, n (%) | 3 (8.3 %) | 83 (17.5 %) | 0.43 (0.13 – 1.43) | 0.25 | | |

95CI, 95 % confidence interval; SD, standard deviation
The following predictors were excluded as no patients had the risk factor of interest and the study outcome: sphincter of Oddi dysfunction and pancreas divisum.

when using a long continuous infusion (more than 12 hours) with at least 3 mg, and when a single bolus injection (250 µg or 4 µg/kg) was given. The two main limitations of this meta-analysis are that not all studies described the randomization sequence, and only three used a bolus infusion.

Although these four meta-analyses suggested that the incidence of pancreatitis decreased with somatostatin prophylaxis, current guidelines do not recommend the use of the drug in this setting [1 – 3]. There may be several reasons for this. The first explanation could be the heterogeneity among studies concerning the treatment regimen (i. e. bolus, infusion, total dosage). Second, a long, continuous infusion is not feasible in many centers as most ERCPs are performed on an outpatient basis and patients are discharged 4 – 6 hours after the procedure. Third, somatostatin is not commercially available worldwide. And fourth, other prophylactic recommendations have recently been included in clinical guidelines [1 – 3]. The first two possibilities were evaluated in this study by using an administration regime that could benefit from the initial bolus effect at the time when the papilla and pancreas were tackled, and that maintained the effect of the drug with a short infusion. This regime did not modify the management of our patients during the post-procedure period, and ensured the total infusion of 1250 µg of somatostatin. However, we did not find any differences in the incidence of post-ERCP pancreatitis or in its severity.

Other prophylactic interventions have proven to be effective in minimizing the incidence of post-ERCP pancreatitis, and have recently been advocated in clinical practice guidelines [1 – 3]. These include nonsteroidal anti-inflammatory drugs (NSAIDs) [21 – 24] and pancreatic stents [25 – 30]. This being so, it seems clear that other prophylactic methods can reduce the incidence of post-ERCP pancreatitis, questioning even further the usefulness of somatostatin prophylaxis.

It could be argued, however, that somatostatin might be effective for high risk patients. In our study, we excluded patients with a low risk of pancreatitis (i. e. previous sphincterotomy, chronic pancreatitis), and additionally performed a second analysis that included only high risk patients, defined as in a recent clinical trial [20]. Even in this second analysis we did not find a reduction in the incidence of pancreatitis.

Additionally, the analyses of independent risk factors for post-ERCP pancreatitis demonstrated statistical association only with younger age. However, the frequency of some of the factors evaluated was too low to reveal statistical significance. For example, pancreatic acinarization was almost tripled in the cases with pancreatitis, but it occurred only in 12 cases. Larger multicenter studies might be of interest to better define risk factors.

The main strength of this study is its large sample size. We included 510 ERCP procedures in a randomized, double-blind clinical trial that evaluated the combined administration of somatostatin (bolus plus continuous infusion), an approach that could theoretically increase the effect of this drug. However, no benefits were observed. It is important to add that there were no patient losses during the trial follow-up. Furthermore, the intervention was similarly implemented for both sexes and for all patients over 18 years, and it was performed by four different endoscopists. Additionally, we excluded patients with a low risk of pancreatitis as they are less likely to benefit from prophylaxis. The results indicate that this prophylactic method is probably ineffective for all populations undergoing an ERCP.

The relatively low dose of somatostatin administered could be a limitation of this study. The most recent meta-analysis hypothesized that a minimum of 3 mg of somatostatin is needed when a 12-hour infusion is administered [18]. However, this recommendation refers to the use of a continuous infusion alone, but not to the approach of using a bolus before the infusion. The low incidence of sphincter of Oddi dysfunction might be another limitation for the study. This is the risk factor that seems to be most strongly associated with post-ERCP pancreatitis. Nevertheless, this might reflect daily clinical practice in most institutions, and, additionally, the study was powered to evaluate an incidence of 7.7 % of pancreatitis, similar to the one observed. Another limitation, common to all studies evaluating post-ERCP pancreatitis, is the imprecision in defining this event. We used a widely accepted definition [19], and all cases where there was disagreement were revised in a group meeting. Additionally, it should be noted that the cases with disagreement were always defined as mild, sug-

gesting that the more severe acute pancreatitis episodes were not affected by this limitation. Finally, another limitation is that the study was powered to detect a 67.5% reduction on the incidence of pancreatitis. This is a considerable reduction; however, multiple previous studies have described similar differences [10, 13, 14, 17, 20]. The reductions observed in these trials ranged from 63% to 76%, and some of them were used to estimate the sample size of our study. Additionally, our trial aimed to detect a possible synergic effect between the bolus and the short infusion. As such, even larger differences were expected.

In conclusion, the administration of a 250 µg intravenous bolus of somatostatin followed by a short continuous infusion (250 µg/h over 4 hours) did not reduce the incidence of post-ERCP pancreatitis. Taking into account the contradictory results of other studies and the current prophylactic methods proposed in guidelines, we cannot recommend the use of somatostatin for this indication.

**Competing interests:** None

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