ORIGINAL PAPERS

Early precut is as efficient as pancreatic stent in preventing post-ERCP pancreatitis in high-risk subjects - A randomized study

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ABSTRACT

Background: The most common adverse event of endoscopic retrograde cholangiopancreatography is pancreatitis. Precut sphincterotomy has been regarded as a risk factor. Some authors have stated that early precut may actually reduce post-ERCP pancreatitis risk. However, early precut as a preventive measure has not been compared to other preventive measures, such as pancreatic duct stent placement.

Aim: To compare the efficacy of early precut sphincterotomy *versus* pancreatic duct stent placement in high-risk subjects undergoing endoscopic retrograde cholangiopancreatography for the prevention of post-endoscopic cholangiopancreatography.

Materials and methods: This was a single-blinded, randomized trial that took place in two tertiary referral centers in Buenos Aires, from November 2011 to December 2013. ERCP subjects presented at least one of the following risk factors: female sex, age less than 40 years, clinical suspicion of sphincter of Oddi dysfunction, previous pancreatitis, and/or common bile duct diameter of less than 8 mm. Only those who presented a difficult biliary cannulation were randomized into two groups: those who received early precut sphincterotomy and those in whom persistency of biliary cannulation was intended, with subsequent pancreatic duct stent placement after cholangiography was achieved. The incidence of post-ERCP pancreatitis, as well as other adverse events incidence, was compared.

Results: Overall, 101 patients were enrolled, 51 in the pancreatic duct stent group and 50 in the early precut group. Pancreatitis rate was similar in both groups (3.92% *vs.* 4%, p NS). In all cases, pancreatitis was classified as mild. There were no deaths registered.

Conclusion: Early precut was associated with an incidence of adverse events similar to pancreatic duct stent placement.

Key words: Precut. Pancreatic stent. Pancreatitis. ERCP.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has become the standard therapeutic procedure for the treatment of different bilio-pancreatic conditions, such as common bile duct stones (1). Among its adverse events, the most common is post-ERCP pancreatitis (PEP), which occurs after 1 to 30% of ERCPs (2). This wide variation may be due to differences in the characteristics of studied populations, or the therapeutic procedures involved during ERCP. As a matter of fact, there is growing evidence showing factors that increase PEP risk (3).

Among these factors, precut sphincterotomy has been regarded as a potential risk factor leading to PEP (4,5). Nevertheless, some publications have suggested that when precut sphincterotomy is performed during early attempts, it does not carry a significant risk for PEP, especially in the setting of difficult biliary cannulation.

Pancreatic duct stent (PDS) placement has been shown to be a prophylactic measure against PEP development, especially in high-risk patients (6). On the other hand, its placement is not always feasible, and it may carry higher costs and a second endoscopic procedure if spontaneous stent dislodgement is not accomplished (7).

Previous studies assessing the efficacy of early precut sphincterotomy as a preventive measure against PEP have shown that it actually reduces PEP risk (8). However, these studies did not compare early precut sphincterotomy against other preventive measures, such as PDS placement. Hence, we sought to compare the efficacy of early precut sphincterotomy and PDS in patients undergoing ERCP with a high risk of developing PEP for the prevention of pancreatitis.

MATERIALS AND METHODS

This was a single-blinded randomized trial that took place in two tertiary referral centers in the Buenos Aires metropolitan area between November 2011 and December 2013. We tried to assess whether performing early precut in a difficult cannulation setting would be as safe as persistency in biliary cannulation with PDS placement. The study protocol was approved by the institutional review board at each center and it was registered in ClinicalTrials.gov (registry number: NCT02497872).

Study population

Consecutive patients were considered for inclusion if they underwent ERCP. Enrolled subjects would present at least one of the following PEP risk factors: female sex, age less than 40 years, clinical suspicion of Sphincter of Oddi dysfunction (SOD), previous PEP, previous acute pancreatitis, and/or common bile duct diameter of less than 8 mm. Patients were excluded for any of the following reasons: age younger than 18 years, pregnancy, and/or coagulopathy. Subjects who fulfilled these criteria were invited to participate and asked to sign an informed consent form.

Study design and technique

ERCPs were performed using Pentax© (Pentax America, New Jersey, USA) or Fujinon© (Fujifilm Corporation LatinAmerica) endoscopes. Patients were sedated by trained anesthesiologists using propofol. ERCPs were performed by four experienced endoscopists who usually perform a minimum of 300 ERCPs per year. Biliary cannulation was attempted using the guide-wire technique by means of a sphincterotome. Once biliary cannulation was achieved, endoscopic sphincterotomy was performed according to previously published techniques. When necessary, precut endoscopic sphincterotomy was performed using needle-knife sphincterotome by cutting 5 to 10 mm cephalad in the 11-to-12 o'clock position, beginning at the papillary orifice with blended current at a setting of 40 W. Once bile duct access was achieved and cholangiography completed, biliary sphincterotomy was completed using a standard pull-type sphincterotome.

Among eligible patients, only those who presented a difficult biliary cannulation were enrolled and randomized into two groups: those who received early precut sphincterotomy (early precut group) and those in whom persistency of biliary cannulation was intended with subsequent PDS placement after cholangiography was achieved (PDS group). Difficult biliary cannulation was defined as persistent attempts for more than eight minutes or involuntary guidewire insertion in the pancreatic duct in more than three opportunities. Randomization was centrally generated by computer sequencing.

Among subjects randomized to the latter group, a 5F or 7F internally and externally flanged straight or internally flanged with an external three-fourths pigtail prophylactic pancreatic duct stent was placed after cholangiography completion. Stent dislodgement was checked after 7 days by means of an abdominal X-ray. In the event of stent persistency, endoscopic removal was undertaken (9).

All patients were admitted after the procedure and discharged the following day. Also, every enrolled subject had serum amylase and complete blood count before discharge.

Outcomes

Our main endpoint was the comparison of PEP incidence between groups. PEP was defined as new-onset or increased abdominal pain that lasted for more than 24 hours and prolonged hospitalization, and was associated with an elevation of serum amylase levels, at least 3 times more than the upper limit of normal levels. The severity of PEP was classified according to previously published criteria by Cotton into three groups: mild, moderate, and severe.

The incidence of other adverse events such as hemorrhage (defined as gastrointestinal bleeding after ERCP that prolonged patient hospitalization, required red blood cell transfusion or caused a decrease of at least 1 g/dl of hemoglobin) and perforation were also compared.

Finally, biliary cannulation success was compared between groups. Reasons for referral, biliary duct stenting and other therapeutic procedures for each ERCP were also collected and compared.

Statistical analysis

According to previously published experiences with PEP high-risk patients, we estimated a PEP incidence of 10% in the pancreatic duct stent group and 30% in the early precut group. Considering a type I error of less than 5% and a type II error of less than 20%, a sample size of 120 (60 patients per group) was calculated in order to detect the aforementioned difference. Due to difficulties in patient enrollment (probably because of the low prevalence of difficult biliary cannulation in tertiary referral centers), we decided to perform a pilot study on 50 patients enrolled per group.

PEP risk factors prevalence was also compared between groups in a univariate analysis. If any unequal distribution was found, a multivariate analysis using a logistic regression model would be performed.

Categorical variables were described as percentages. Odds ratios (OR) with their 95% confidence intervals (95%CI) were calculated. Numerical variables were described as means with their standard deviation. PEP incidence and other adverse events incidence were compared using the Chi-squared test. For comparison of numerical variables, the Student's t test was used. Statistical analyses were performed using Stata software (Stata v11.1; Statacorp, College Station, Texas, USA).

Outcome comparison was performed using an intention-to-treat analysis, including all enrolled and randomized subjects, even if ERCP could not be completed. A p value of less than 0.05 was considered as statistically significant. Patients who were invited to participate but did not accept to sign the informed consent form were not included in the intention-to-treat analysis.

RESULTS

During the study period, 1,498 patients undertaking ERCP were screened. Of these, 101 patients who fulfilled inclusion criteria were finally enrolled: 51 in the pancreatic duct stent group and 50 in the early precut group. It is worth mentioning that 30 patients were invited to participate but declined and did not sign the informed consent form, as seen in figure 1. We enrolled 101 patients due to the difficulties found in recruiting patients who fulfilled eligibility criteria throughout a pre-specified schedule, determined by the principal investigators. Table I shows baseline characteristics and indications for ERCP. Mean age was 51 ± 15 years and 69% were female patients. The most frequent reason for referral in both groups was common bile duct stone obstruction. As it can be seen, we found no significant differences in the prevalence and dis-
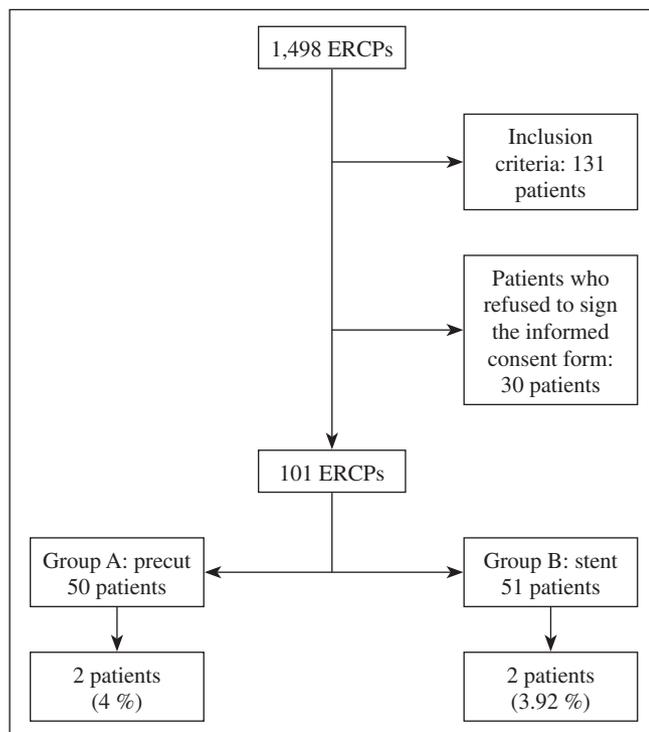
Fig. 1.

tribution of the enrolled patients PEP risk factors. Table II shows the comparison of therapeutic procedures performed in both groups. Overall, successful biliary cannulation was completed in 49 out of 51 patients in the PDS group and 49 out of 50 patients in the early precut group (failed cannulation rate = 3.92% *vs.* 2% , OR 2 [0.78-22.78], p NS). In cases in which a pancreatic stent placement was intended, this was successfully accomplished.

Table III shows the comparison of procedure-related adverse events. PEP rate was similar in both groups (3.92% *vs.* 4%, p NS). In all cases, pancreatitis was classified as mild. There were no deaths registered. No patient was lost at follow-up. No significant difference was found between other PEP adverse events incidence between groups. Two patients experienced duodenal perforation: in both cases, management was both endoscopic (deployment of a 10 Fr biliary plastic stent) and medical (N.P.O. and antibiotics). Both patients were successfully discharged afterwards.

DISCUSSION

The results of our study show a similar incidence of PEP between subjects undergoing early precut sphincterotomy and those undergoing PDS placement after cholangiogra-

Table I. Main characteristics of enrolled patients in early precut and pancreatic duct stent placement groups

	Early precut (n = 50)	Pancreatic duct stent (n = 51)	OR (CI 95%)	p
Age*	52 ± 15.51	49 ± 16.68	N/A	0.43
Sex (% F)	68	70.59	0.88 (0.37-2.06)	0.83
SOD (%)	2	0	N/A	N/A
Reason for referral				
Common bile duct stones (%)	78	82.29	0.76 (0.28-2.03)	0.62
Malignant biliary obstruction (%)	22	17.71	1.31 (0.49-3.51)	0.62
Prior acute pancreatitis (%)	6	13.72	0.4 (0.09-1.65)	0.31
History of recurrent pancreatitis (%)	2	1.96	1.02 (0.06-16.77)	1
Billirubin < 1 mg/dl (%)	12	13.72	0.85 (0.26-2.75)	1
Yuxtapapillary diverticula (%)	2	1.96	1.02 (0.06-16.77)	1

*Results expressed as mean ± standard deviation. SOD: Sphincter of Oddi dysfunction.

Table II. Comparison of therapeutic procedures performed in each group

	Early precut (n = 50)	Pancreatic duct stent (n = 51)	OR (CI 95%)	p
Biliary stent (%)	20	15.68	1.34 (0.48-3.74)	0.61
Sphincteroplasty (%)	10	9.81	1.02 (0.27-3.77)	1
Stone extraction w/dormia basket (%)	56	50.98	1.22 (0.56-2.67)	0.69
Stone extraction w/balloon (%)	10	13.72	0.69 (0.21-2.36)	0.76
Other interventions (%)	4	3.92	1.02 (0.13-7.54)	1

Table III. Comparison of ERCP-related adverse events between groups

	Early precut (n = 50)	Pancreatic duct stent (n = 51)	OR (CI 95%)	p
Post-ERCP pancreatitis (%)	4	3.92	1.02 (0.13-7.54)	1
Abdominal pain (%)	6	5.88	1.02 (0.19-5.31)	1
Bleeding (%)	2	0	N/A	N/A
Cholangitis (%)	0	0	N/A	N/A
Perforation (%)	2	0	N/A	N/A
Death (%)	0	0	N/A	N/A

phy completion. This observation shows that early precut sphincterotomy is non-inferior to the most extensively studied endoscopic measure against PEP.

As aforementioned, PEP incidence increases with the presence of certain risk factors (3). The identification of such factors is relevant because it can help endoscopists to determine the basal risk a patient may have of developing a dreadful adverse event such as PEP. Among these, precut sphincterotomy has been pointed out as a possible risk factor. On the contrary, when applied at an early stage, precut sphincterotomy does not seem to confer a significant PEP risk. As a matter of fact, a meta-analysis by Cennamo et al. (8) showed that early precut sphincterotomy may result in a lower risk of PEP, when compared to persistent attempts of achieving biliary cannulation. This may underscore the fact that persistence in biliary cannulation may actually be a risk factor for developing PEP and not precut sphincterotomy (10).

However, most studies assessing this particular subject have compared an early precut strategy against a more conservative approach of persistence in biliary cannulation. To our knowledge, no previous study has compared the preventive potential of early precut sphincterotomy against other preventive measures. These measures can be divided into two main groups: prophylactic medications, such as rectally-administered indomethacin and, on the other hand, endoscopic measures, mainly PDS placement (9-11-14 n).

PDS has been extensively studied as a prophylactic measure against PEP (6). In fact, its placement is recommended when performing ERCP in high-risk patients (15). However, much less evidence exists regarding its use in patients with a low risk of PEP and as a consequence, its extensive use is still under debate (16). Some disadvantages regarding PDS placement are worth mentioning. First of all, its placement is not always feasible, even in experienced hands. It also may carry higher costs, especially if we consider that many times a second endoscopic procedure is needed if spontaneous dislodgement of the PDS is not accomplished.

According to our results, early precut sphincterotomy, especially when performed by experienced hands, was not associated with an increased risk of PEP. This is relevant because it was compared against what it may be considered as the "gold-standard" prophylactic measure in PEP.

A number of strengths in our study should be mentioned; first of all, patients were carefully selected in order to show the impact these interventions may have in patients at risk. Moreover, we followed a randomized controlled design and analyzed the data using an intention-to-treat analysis. Some limitations should be taken into account: the sample size was not large enough according to our estimations and the rigorous inclusion and exclusion criteria made the enrollment process really cumbersome. Obviously, this limitation has an important impact on the validity of our results; however, we think that these results have relevance regardless of the relatively low sample size, since it does not show a profound tendency towards the benefit of what has been suggested as the state-of-the-art prophylactic measure against PEP (which is pancreatic stenting), and thus, it may serve as an example for further larger controlled trials on this subject.

In conclusion, early precut sphincterotomy is associated with an incidence adverse event similar to those patients receiving PDS placement. This study highlights the potential preventive efficacy of early precut sphincterotomy against PEP.

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