

ORIGINAL PAPERS

Post-ERCP pancreatitis: early precut or pancreatic duct stent? A multicenter, randomized-controlled trial and cost-effectiveness analysis

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ABSTRACT

Background: Pancreatitis is the most frequent complication due to ERCP. Pancreatic duct stent placement has been described as a preventive measure. There is also evidence pointing towards the preventive effect that early precut may provide.

Aim: To determine and compare the cost-effectiveness of an early precut approach versus pancreatic duct stent placement for the prevention of post-ERCP pancreatitis.

Methods: This was a multicenter, randomized-controlled pilot study with a cost-effectiveness analysis performed between early precut (group A) and pancreatic duct stent (group B) for the prevention of pancreatitis in high-risk patients. Patients with a difficult biliary cannulation and at least one other risk factor for post-ERCP pancreatitis were enrolled and randomized to one of the treatment arms. Both effectiveness and costs of the procedures and their complications were analyzed and compared.

Results: From November 2011 to November 2013, 101 patients were enrolled; 50 subjects were assigned to group A and 51 to group B. There were no significant differences in terms of baseline characteristics of patients between groups. Two cases of mild pancreatitis were observed in each group. The overall costs were U\$ 1,242.6 per patient in group A and U\$ 1,606.5 per patient in group B. The cost in group B was 29.3% higher ($p < 0.0001$).

Conclusion: Early precut showed a better cost-effectiveness profile when compared to pancreatic duct stent placement.

Key words: Early precut. Pancreatic duct stent. Post-ERCP pancreatitis. ERCP. Precut. Post-ERCP complications.

INTRODUCTION

Pancreatitis is the most common adverse event after an endoscopic retrograde cholangiopancreatography (ERCP). Its incidence varies between 1-7% and can reach values of up to 25% in high-risk patient groups. The vast majority of post-ERCP pancreatitis (PEP) are mild or moderate; however, 1-5% of patients may develop severe pancreatitis which may result in prolonged hospitalization and the need for endoscopic or surgical procedures (1-4).

There have been several lines of investigation related to PEP prevention. There are several pharmacologic agents that were tested for this purpose, most of them showing disappointing results, except for rectal indomethacin or diclofenac (5). On the other hand, pancreatic duct stent deployment during ERCP in high-risk subjects has been proposed as an effective prophylactic measure (6-11). A meta-analysis published by Mazaki et al. in 2014 included 14 randomized-controlled trials and observed a significant reduction of PEP incidence (RR = 0.39 [0.29-0.53]) in favor of pancreatic duct stent placement among high-risk subjects (patients with sphincter of Oddi dysfunction, difficult biliary cannulation, pancreatic sphincterotomy, precut sphincterotomy, sphincteroplasty or endoscopic ampullectomy) (12). A cost-effectiveness analysis of pancreatic duct stent placement regarding prevention of PEP showed that this approach exhibited a good cost-effectiveness profile only when considering high-risk patients (13).

Patients with difficult biliary cannulation constitute a group with a significant risk for the development of PEP. Difficulties in biliary cannulation can occur in up to 5 to 15% of ERCPs. Precut sphincterotomy is a technique that can be used in this endoscopic scenario, but has been associated with a non-negligible incidence of adverse events (16,17). Some authors suggest that the complications following precut sphincterotomy (especially PEP) may be due to papillary trauma as a result of multiple attempts to cannulate the biliary duct or due to the involuntary cannulation of the pancreatic duct (18). This raised the hypothesis that early precut may even act as a potential prophylactic measure against PEP in patients with a difficult biliary cannulation (17,19,20). Cennamo et al. published a meta-analysis of randomized-controlled trials comparing both successful cannulation incidence as well as complication incidence between early precut and persistence in biliary cannulation with a standard technique. Six studies were included, and

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pooled analysis showed a successful cannulation rate of 90% in both groups, but with a significantly lower risk of PEP in the early precut group (OR = 0.47 [0.24-0.91]) (21).

To our knowledge, there is only one published trial comparing early precut *versus* pancreatic duct stent placement as PEP prophylactic measures (22). This trial showed that early precut was non-inferior to pancreatic duct stent for this purpose. There are no published studies assessing the comparative cost-effectiveness of both techniques in high-risk patients presenting with difficult biliary cannulation. Hence, we sought to determine the cost-effectiveness of the aforementioned techniques in the setting of high-risk patients undergoing ERCP with difficult biliary cannulation.

MATERIAL AND METHODS

Design

This was a multicenter, prospective, randomized-controlled pilot study, with cost-effectiveness analysis comparing the use of the early precut technique *versus* pancreatic duct stent placement for the prevention of PEP in high-risk subjects with a difficult biliary cannulation.

Enrolled patients were randomized into the following treatment arms:

- Group A: early precut sphincterotomy.
- Group B: pancreatic duct stent placement (with or without precut).

Study population

This study was undertaken in two public tertiary referral centers in the Buenos Aires metropolitan area between November 2011 and November 2013.

Inclusion criteria were age > 18 years and difficult biliary cannulation, with at least one of the following PEP risk factors: female gender, age < 40 years, clinical suspicion of sphincter of Oddi dysfunction, history of previous acute pancreatitis and/or non-dilated common bile duct (< 8 mm).

Patients with previous sphincterotomy, coagulation disorders, altered bilio-pancreatic anatomy or those unavailable for further follow up were excluded.

Difficult biliary cannulation was defined as the impossibility to cannulate the common bile duct after eight minutes, or guide-wired-cannulation of the main pancreatic duct at least twice or contrast injection into the main pancreatic duct.

Early precut sphincterotomy was performed immediately after randomization. Late precut was performed after eight minutes of attempting a biliary cannulation. All the enrolled subjects signed an informed consent. The study protocol was approved by the Ethics Committees at both institutions and all investigators were committed to follow the Ethics recommendations described in the Declaration of Helsinki of 1975 (reviewed in 2013).

Procedure description

ERCP

This procedure was performed by expert endoscopists with adequate experience (> 300 ERCPs/year). Fujinon® Therapeutic duodenoscopes were used (4.2 mm channel, Series 450) (Fujifilm Corporation Latin America) as well as Pentax® duodenoscopes (Pentax America, New Jersey, USA). Patients were sedated using fentanyl, propofol and succinylcholine; orotracheal intubation was used in every case.

Selective biliary cannulation was attempted by means of a sphincterotome (Tritome PC Triple Lumen, Cook, Indiana, USA) using the guide-wire technique (Jagwire Straight Tip, Boston Scientific, Boston, Massachusetts, USA). If eligibility criteria were fulfilled, patients were randomized during the ERCP into one of the following treatment arms:

- Group A: early precut sphincterotomy was performed. The endoscopist in each case chose the most appropriate precut technique to be performed: septotomy, infundibulotomy, standard precut.
- Group B: a 5-7 Fr pancreatic stent, 3 to 5 cm long and with internal flaps or a pigtail with internal flap, was placed with or without late precut.

Sphincterotomies as well as precut sphincterotomies were performed with an electrosurgical source (Emed ES 350) using pure cut mode at 50 W. Precut sphincterotomies were performed with Microknife XL Triple Lumen (Boston Scientific, Massachusetts, USA).

Follow up

After the ERCP procedure, patients were admitted to the hospital for 24 hours. After discharge, they were controlled in the outpatient clinic or by telephone contact a week later. Those patients with pancreatic duct stent placement were evaluated with abdominal x-rays to check for stent migration. In case of stent persistence, these would be endoscopically removed.

Adverse effects

Post-ERCP pancreatitis: this was defined as the occurrence of intense and continuous abdominal pain, with an increase in amylase levels > 3 times the normal upper limit value during the first 24 hours after the procedure, and/or pancreatic swelling with glandular enlargement as observed by an adequate imaging test (23,24).

Post-ERCP bleeding: this was defined as the presence of melena with or without hemodynamic compromise, or the decrease in the value of hemoglobin by at least 2 g/dl, or the need for red blood cell transfusion after the procedure.

Perforation: this was defined as the presence of pneumoperitoneum or retroperitoneum by an adequate imaging test with the accompanying clinical presentation.

The severity of these adverse events are further described in table I.

Table I. Classification of the severity of ERCP-related adverse events (23)

	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Pancreatitis	Typical abdominal pain and amylasemia increase > 3 times the upper normal value 24 hours after ERCP Requires hospital admission for less than three days	Pancreatitis that requires hospital admission for 4-10 days	Pancreatitis that requires hospital admission for > 10 days, or presence of local complications or need for intervention
Bleeding	Hematemesis or melena Hemoglobin decrease of less than 2 g/dl No need for red blood cell transfusion	Red blood cell transfusion (four units or less) No need for angiographic or surgical treatment	Red blood cell transfusion (> 5 units) Need for angiographic or surgical treatment
Perforation	Possible perforation or minor contrast leak (o minor collection) treatable with IV hydration, diet restriction and antibiotics for < 3 days	Perforation confirmed by Rx, with medical treatment for 4-10 days	Medical treatment for > 10 days or need for intervention (surgical or non-invasive drainage)

Cost analysis

For this variable the following aspects were estimated: cost of ERCP, number of necessary interventions, length of hospital stay, pancreatic duct stent costs, as well the costs related to outpatient clinic assessment, x-rays and the eventual endoscopic extraction of stents. Table II describes the aforementioned costs. It is worth mentioning that in our healthcare system, the costs related to ERCP with anesthesia support include all the necessary materials for the procedure except for metallic or plastic stents and balloons.

Sample size estimation

According to previously published data in PEP high-risk patients, we estimated a projected PEP incidence of 10% in the pancreatic stent group and 30% in the early precut group. Considering an alpha error of less than 5% and a beta error of less than 20%, 120 patients (60 patients per treatment arm) would be sufficient to detect the above-mentioned difference.

Randomization

A centrally-generated, computer based simple randomization was performed. This was done by means of the Research Randomizer software. The randomization list was uploaded to the web so that

it was readily available for the allocation of patients at both institutions.

Statistical analysis

Epi Info (version 3.1.2) was used for statistical analysis. Categorical variables were compared using the Chi-squared test or Fisher's test, when appropriate. Student's t-test or Mann-Whitney test were used for the comparison of numerical parametric and non-parametric variables, respectively; 95% confidence intervals were estimated. A p value of less than 0.05 was considered as statistically significant.

RESULTS

From November 2011 to November 2013, 1,498 ERCPs were performed. We initially screened 131 patients who fulfilled the inclusion criteria, but only 101 patients signed the informed consent and, consequently, were enrolled in the study. Fifty patients were randomized to the early precut group and 51 to the pancreatic duct stent group. There were no significant differences in terms of demographic features, reason for referral or PEP risk factors between groups, as seen in table III.

ERCP procedure

Successful biliary cannulation was achieved in 98% (49/50) of patients from group A and in 96% (49/51) of patients from group B. The three patients in which initial biliary cannulation was not achieved were subject to a subsequent endoscopic intervention that proved to be successful in every case. The latter procedures were also contemplated in the overall costs of each group. All the enrolled patients had their biliary condition resolved endoscopically. There were no significant differences in terms of the therapeutic interventions needed between groups (biliary stent deployment, sphincteroplasty, biliary stone retrieval).

Table II. Costs of procedures, hospital admission and materials

<i>Item</i>	<i>Cost</i>
ERCP with anesthesia (pancreatic duct stents not included)	U\$ 1,193
Hospital admission (per day)	U\$ 620
Pancreatic duct stent	U\$ 181
Outpatient control and abdominal x-ray	U\$ 32.5
Duodenoscopy for stent retrieval	U\$ 193

Source: Cost Department, Hospital de Alta Complejidad El Cruce.

Table III. Characteristics of enrolled subjects

Variables	Early precut (n = 50)	Pancreatic duct stent (n = 51)	p
<i>Demographic features</i>			
Age	52 ± 15.51	49 ± 16.68	NS
Gender (F/M)	34/16	36/14	NS
<i>Reason for referral</i>			
Choledocolithiasis (%)	15 (30%)	24 (47%)	NS
Biliary duct obstruction (%)	24 (48%)	18 (35.3%)	NS
Other (acute pancreatitis, gall-bladder cancer, etc., %)	11 (22%)	9 (17.6%)	NS
<i>PEP risk factors</i>			
< 40 years (%)	9 (18%)	12 (23.5%)	NS
Non-dilated common bile duct (%)	4 (8%)	2 (3.92%)	NS
Previous acute pancreatitis (%)	3 (6%)	7 (13.7%)	NS
Recurrent pancreatitis (%)	1 (2%)	1 (1.96%)	NS
Juxtadiverticula papillary (%)	1 (2%)	1 (1.96%)	NS

N/A: Non applicable; NS: Non significant (Fisher's test or Chi-squared test).

Adverse events

There were two cases of PEP in each group, all of them mild and each of them required two days of admission (OR 1.02 [0.13-7.54]). There were two cases of post-ERCP bleeding in group A: one of them responded after adrenaline injection (1:20,000) without the need for further hospital admission and the other one ceased spontaneously. There were two perforations in group A, both of them related to the therapeutic approach of biliary stenosis. Although these perforations were not directly related to the precut procedure, we included the costs derived from the care of such cases in our cost-effectiveness analyses.

Cost-effectiveness analysis

The cost of the endoscopic procedures in group A (early precut) was US\$ 59,650. In addition, the cost of the two admissions due to mild PEP was US\$ 2,480. Hence, the overall costs in group A was US\$ 62,130 (US\$ 1,242.6 per patient). This estimation does not include the cost related to the cases of biliary perforations mentioned previously: if this was included, then the cost of admission (US\$ 8,680 for both patients), antibiotic therapy (US\$ 252 for both patients) and CT scans (US\$ 717.3 for both patients) would give a final cost of US\$ 71,775.3 (US\$ 1,435.5 per patient).

The cost of endoscopic procedures in group B, including pancreatic duct stent placement, was US\$ 70,074. Additionally, the cost of the two hospital admissions due to mild PEP was US\$ 2,480. Furthermore, the cost associated with outpatient follow up and radiological confirmation of stent dislodgement plus endoscopic retrieval of pancreatic

stents in 40 patients was US\$ 7,720 (11 patients had spontaneous stent migration). The overall cost in group B was US\$ 81,931.5 (US\$ 1,606.5 per patient).

The comparison of the overall costs between groups showed a significant difference ($p < 0.0001$); the cost implicated in group B was 29.3% higher when compared to group A, without considering the cost of the medical care of the patients with perforations. If the latter were included, the difference was still significantly different: the cost implicated in group B was an 11.9% higher than the cost implicated in group A ($p < 0.0001$).

DISCUSSION

The hypothesis that PEP in patients with a difficult biliary cannulation in which precut sphincterotomy is used could actually be caused by the papillary edema due to the numerous attempts of cannulation was proposed by the study published by Zagalsky et al. (22). This study actually suggests that early precut is not inferior to what is considered to be the "gold-standard" in terms of PEP prophylaxis, that is to say pancreatic duct stent placement. Based on these findings, our study aimed to analyze both approaches for high-risk patients from a cost-effectiveness point of view.

The relatively low incidence of PEP in the population studied (4% vs 3.96%), even though they were patients with risk factors for PEP, highlights the importance of a rapid approach to biliary cannulation, which results in less papillary damage and thus behaves as a prophylactic measure itself.

The meta-analysis published by Cennamo et al. shows that an early precut strategy when facing a possible diffi-

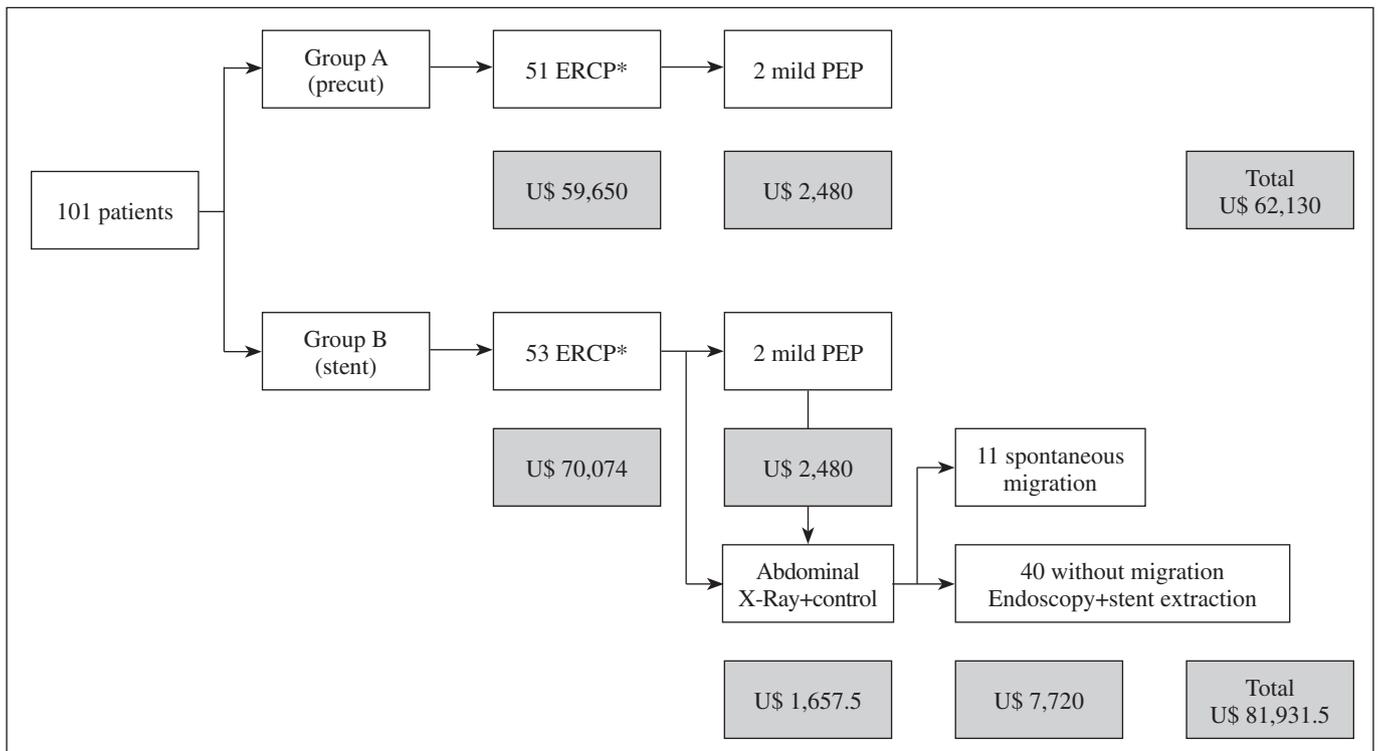


Fig. 1. Flow Diagram of group A and B procedures and their costs. Boxes in gray detail the costs of the above-mentioned procedures. *One patient in group A and 2 patients in group B had to undergo a subsequent ERCP due to cannulation failure, with successful biliary cannulation in the second attempt.

cult biliary cannulation could reduce PEP incidence. It is very likely that the trauma originated due to the persistence of cannulation by a conventional method and the number of involuntary cannulations, or even contrast injections in the pancreatic duct, could be responsible for the increased risk of PEP (19).

On the other hand, Mazaki et al. published a meta-analysis assessing the efficacy of pancreatic duct stent placement for the prevention of PEP; they found a pooled relative risk of 0.39 (0.29-0.53), which shows that this technique is effective as a preventive measure against PEP, especially in high-risk patients (12).

In the study published by Das et al., the authors suggest that this approach has a good cost-effectiveness profile when considering patients with a high risk of developing PEP.

Our study compared an early precut approach *versus* pancreatic duct stent in high-risk patients; we found no significant differences in the incidence of PEP. Additionally, although no differences were found in terms of preventive efficacy among high-risk patients, we found significant differences in the costs of each approach.

To our knowledge, this is the first cost-effectiveness study comparing both techniques. In the pancreatic duct stent group the higher costs can be explained by the inherent costs of the pancreatic stents, the follow up to check

if spontaneous dislodgement of the stent has occurred and the endoscopic procedures for stent retrieval. It is worth mentioning that in the early precut group, two perforations occurred that did not have a direct association with precut sphincterotomy; even so, if the costs generated by the medical treatment of such complications (hospital admission, antibiotic therapy, CT scans) are also included in the analysis, early precut is still a more suitable approach from a cost-effectiveness perspective.

The limitations should be mentioned. First of all, the relatively small sample size of enrolled patients may underestimate the true incidence of complications; however, there is no tendency towards any difference between both approaches. On the other hand, the costs of procedures, materials and hospital admissions were based on the references provided by public hospitals; significant differences may exist if we consider private hospitals' costs. It is important to stress that this was a multicenter, randomized controlled trial in a high-risk population.

In conclusion, both early precut and pancreatic duct stent placement seem to behave in a similar way as preventive measures against PEP in high-risk patients with a difficult biliary cannulation. However, the pancreatic duct stent placement approach implicated a 29% increased cost when compared to early precut.

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