Dose needle-knife precut sphincterotomy and repeated cannulation correlate with post-ERCP pancreatitis in patients with bile duct stone disease?

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Background
Pancreatitis is the most common and serious complication that occurs after endoscopic retrograde cholangiopancreatography (ERCP), resulting in substantial morbidity and occasional mortality. Biliary cannulation is unsuccessful during 5–10% of ERCP procedures. Needle-knife sphincterotomy can improve the success of cannulation but is often used as a last resort.

Aim
The aim of this study was to assess the role of precutting and multiple cannulations in the occurrence of post-ERCP pancreatitis in patients with bile duct stone disease.

Patients and methods
This prospective randomized study was performed at the General Surgery Department of Sohag University Hospital between June 2012 and June 2014. It included 515 patients with bile duct stone disease who were subjected to ERCP. Pancreatitis rate was assessed in relation to the number of cannulation attempts (<10 and ≥10) and precutting.

Results
Cannulation was performed without precutting in 467 cases (90.7%) and with precutting in 48 cases (9.3%). Pancreatitis occurred in 9.21% of patients who had undergone biliary cannulation without precutting and in 18.75% of patients who had undergone biliary cannulation with precutting ($P = 0.006$). Pancreatitis rate was lower in patients with less than 10 attempts than in those with 10 or greater attempts at cannulation ($P < 0.0001$), either without ($P < 0.0001$) or with precutting ($P < 0.01$). Pancreatitis rate did not differ without and with precutting when less than 10 attempts at cannulation were performed, whereas it was lower when precut was performed before 10 attempts than when 10 or more attempts were made without precutting ($P = 0.02$).

Conclusion
Pancreatitis rate was lower when precut was performed with less than 10 attempts than when 10 or greater attempts were made without precutting. In experienced hands, precut biliary sphincterotomy does not seem to be an independent risk factor for post-ERCP pancreatitis in patients undergoing ERCP for bile duct stones.

Keywords:
endoscopic retrograde cholangiopancreatography, precut sphincterotomy, repeated cannulations

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most complex endoscopic procedures [1]. The reported incidence of ERCP-specific complications ranges from 5 to 15%, depending on the complexity of the procedure, the underlying diagnosis, and patient comorbidities [2,3]. Acute pancreatitis remains the most common and serious complication after ERCP, with reported incidence ranging from 1.3 to 15.1% in most prospective series, resulting in substantial morbidity and occasional mortality [2,4–9]. Post-ERCP pancreatitis (PEP) is defined as acute pancreatitis that has developed *de novo* following ERCP [8,10]. The mechanisms that lead to PEP are complex and not fully understood. Rather than having a single pathogenesis, PEP is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, microbiologic, and thermal factors [11].

Prospective studies have identified specific risk factors, either patient-related or procedure-related, associated with a higher incidence of PEP [8–12]. Repeated attempts at cannulating the papilla and 'needle-knife' precut sphincterotomy are recognized procedure-related risk factors and occur frequently because biliary

cannulation may fail in up to 15% of cases, even in experienced hands; they therefore have a substantial impact on PEP rate. Although multiple cannulations has been widely considered as an independent risk factor for postprocedure pancreatitis, there are still conflicting data on the risk related to needle-knife sphincterotomy. In a recent prospective Italian multicenter study conducted in high-volume and low-volume centers for ERCP procedures, the PEP rate was found significantly increased when 10 or more attempts at cannulation were made [13]. A cutoff of 10 attempts at cannulation for a significantly increased risk for PEP was also found in a previous study that proposed a four-point risk score for the number of cannulations [14].

Since precutting generally follows a number of failed cannulation attempts, it is hard to clarify whether precutting as such or repeated cannulation is the prime culprit in postprocedure pancreatitis. There are few studies comparing the risk for PEP after 'needle-knife' precut sphincterotomy or persistent attempts at biliary cannulation with the standard technique [15–18].

Aim of the work

The aim of this study was to assess the role of precutting and multiple attempts of cannulation of the papilla of Vater, adjusted for the number of attempts at cannulation (<10 and ≥10), in the occurrence of postprocedure pancreatitis, in a prospective evaluation of a consecutive series of patients who had undergone biliary cannulation and sphincterotomy for bile duct stones.

Patients and methods

This prospective study was performed on 515 patients referred to the Gastrointestinal Endoscopy Unit of Surgery Department of Sohag University Hospital, between June 2012 and June 2014.

The inclusion criteria were as follows:

(a) Presence of bile duct stone disease pre-endoscopically evidenced by clinical manifestations, elevated direct serum bilirubin, and abdominal imaging or the presence of bile duct stone disease demonstrated by cholangiography during ERCP, and
(b) Successful biliary cannulation and sphincterotomy.

Patients were excluded for any of the following reasons:

(a) Pregnancy;
(b) Contraindication to ERCP (coagulopathy, history of contrast dye anaphylaxis, severe cardiopulmonary disease, or recent myocardial infarction);
(c) Acute pancreatitis, cholangitis, or hyperamylasemia at the time of the procedure;
(d) Previous biliary sphincterotomy; or
(e) Need for urgent ERCP within 12 h.

Ethical committee approval and informed written consent were taken before conducting the study.

All patients were subjected to complete assessment including proper history, clinical examination, laboratory investigations (complete blood count, serum bilirubin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, serum albumin, prothrombin time, platelet count, urea and creatinine, blood sugar, and serum amylase), and imaging studies (ultrasound, computed tomography, MRI, or magnetic resonance cholangiopancreatography).

Endoscopic procedure

All ERCP procedures were performed by a high-volume endoscopist using the pentax lateral view endoscope ED-3440T and ED-3485T. Patients were placed in the prone position and sedated with midazolam and propofol in conjunction with a topical anesthetic applied to the posterior oropharynx under the supervision of an anesthesiologist. Deep biliary cannulation was achieved either by direct injection of the contrast agent or by advancing a hydrophilic guide wire, preloaded into the sphincterotome. The decision of whether and when to make the precut was made by the operator. The precut was performed using the freehand technique, starting ~5 mm above the papillary orifice, with a bottom-up cut (fistulotomy). In all cases, a low-osmolality nonionic radiological contrast medium (urografin 76%) was injected for ductal opacification.

All patients were admitted to the hospital at least for 24 h following the procedure to detect early complications. All patients were monitored at least for 6 h after the procedure to detect symptoms and signs of pancreatitis (e.g. abdominal pain, tachycardia, hypotension, fever, and vomiting). Measurement of serum amylase was carried out by sampling of blood at 4 h after ERCP. Abdominal ultrasonography was routinely performed for all patients suffering from pancreatic-like pain lasting at least 24 h. In cases of doubt of developing PEP, abdominal computed tomographic scan was performed. If complications arose, patients stayed in the hospital until they recovered.

Successful cannulation was defined as free and deep instrumentation of the biliary tree. A cannulation

attempt was defined as sustained contact between the cannulating device and the papilla for at least 5 s [19]. Pancreatitis was defined as a postprocedure, new-onset, or increased abdominal pain persisting for at least 24 h, with serum amylase at least three times the upper limit of normal [20]. Amylase values have been found to peak between 90 min and 4 h after ERCP [21]. The serum amylase level measured 4 h after the procedure is the most reliable predictor of PEP [22,23]. We therefore hypothesized and used the 4 h amylase level as the most accurate amylase value for predicting subsequent pancreatitis. Pancreatitis was classified as mild, moderate, or severe according to the criteria of the Atlanta International Symposium of 1992 [24].

Statistical analysis

Data were analyzed using the software package SPSS 15 (SPSS Inc., Chicago, Illinois, USA). Groups were compared using the Mann–Whitney *U*-test and the χ^2-test, as appropriate. Significance was accepted at the 5% level ($P < 0.05$).

Results

This prospective study included 515 patients with bile duct stone disease who fulfilled the inclusion criteria. Attempted biliary cannulation without precut was performed in 467 patients (90.68%). Among these cases, 432 cases (92.51%) required less than 10 attempts, whereas the remaining 35 cases (7.49%) required 10 or more cannulation attempts (Table 1).

'Needle-knife' precut sphincterotomy was required to reach the common bile duct (CBD) in the remaining 48 patients (9.32%). Precutting was associated with fewer than 10 attempts at cannulation in 31 cases (64.58%), and with 10 or more in the other 17 cases (35.42%) (Table 1).

Patients in both groups were matched for age, sex, CBD dilation, serum bilirubin, pancreatic duct opacification, and cannulation technique, with the exception of patients who had undergone precutting, in whom cannulation was attempted mainly with guide wire assistance.

Table 1 Technical details of the procedures

ERCP procedure	Biliary cannulation without precutting		Biliary cannulation with precutting	
Number of attempts	<10	≥10	<10	≥10
Number of procedures	432	35	31	17

Post-ERCP pancreatitis

The overall postprocedure pancreatitis rate was 10.1% (52/515 cases). Pancreatitis occurred in 43 patients (9.21%) in whom precutting was not performed and in nine patients (18.75%) in whom it was performed, independent of the cannulation technique. The incidence of PEP was significantly higher after precutting ($P = 0.006$).

In cases without precutting, the pancreatitis rate was significantly lower ($P < 0.0001$) when fewer than 10 attempts at cannulation were needed than when 10 or more were made. Similarly, after the precut procedure, the pancreatitis rate appeared significantly lower with fewer than 10 attempts than after 10 or more ($P < 0.01$) (Table 2).

Successful biliary cannulation needing 10 or more attempts was associated with four times greater risk for PEP, compared with fewer than 10 attempts. The risk for postprocedure pancreatitis was similar for cases in which the biliary ductal system was cannulated with or without precutting before 10 attempts had been made.

When 10 or more attempts were needed, with or without precutting, the pancreatitis rate was significantly higher. In these cases, precutting did not significantly affect the incidence ($P = 0.45$). However, precutting before 10 attempts at cannulation was significantly less risky compared with 10 or more attempts without precutting.

Discussion

An unsettled question about 'needle-knife' sphincterotomy is whether or not the reported procedure-related high risk for pancreatitis depends on the technique itself or merely reflects the fact that cannulation was difficult, with repeated attempts that may have caused papillary edema, and/or repeated contrast injection into the pancreatic ductal system [25–27].

Table 2 Pancreatitis rates in relation to the number of attempts at cannulation, with and without precutting

Cannulation technique	Cannulation attempts <10 [*n*/*N* (%)]	Cannulation attempts ≥10 [*n*/*N* (%)]	Total [*n*/*N* (%)]	*P* value
Biliary cannulation without precutting	33/432 (7.64)	10/35 (28.57)	43/467 (9.21)	<0.0001
Biliary cannulation with precutting	3/31 (9.68)	6/17 (35.29)	9/48 (18.75)	<0.01
Total	36/463 (7.77)	16/52 (30.77)	52/515 (10.1)	<0.0001

Two studies found that delaying the precut increased the risk for PEP [28,29], whereas four others did not [15,30–32]. Four studies showed that the complication rate of early precut did not exceed that of the standard technique in experienced hands [33–35]. Moreover, Ayoubi *et al.* [36] concluded that, in experienced hands, needle-knife precut sphincterotomy decreases the frequency of PEP.

A recent prospective study stated that the timing of the precut procedure did not influence the complication rate for ERCPs [17]. In contrast, Choudhary *et al.* [37] showed that early precut for CBD cannulation decreases the incidence of PEP.

A meta-analysis of six randomized, controlled trials showed that the precut reduced the risk for pancreatitis compared with conventional technique [38], whereas another recent one suggests that precut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates. Early precut implementation does not increase PEP complications [39]. Fiocca *et al.* [40] suggested that, in cases of difficult papillary cannulation after five failed attempts, performing precut is safe and is associated with a high success rate of deep biliary cannulation with a low incidence of PEP.

Most of these studies were conducted in high-volume centers by experienced endoscopists and indicated that both precut sphincterotomy and repeated attempts give similar success and complication rates in cases of difficult biliary cannulation. In contrast, in prospective multicenter trials in tertiary referral centers and community-based practices with endoscopists of varying levels of expertise, the precut has been shown to be an independent risk factor for overall complications and pancreatitis, with adjusted odds ratios of 3.61 and 4.34 [4] and relative risk of 1.87 and 2.80, respectively [5].

Our study assessed the PEP rate in relation to a cutoff number of 10 attempts at cannulation and the timing of precutting in a large series of consecutive patients undergoing therapeutic ERCP for documented bile duct stone disease. Repeated attempts at papillary cannulation, independent of pancreatic duct cannulation, were confirmed as a significant risk factor for postprocedure pancreatitis; 10 or more attempts at cannulation increased the rate four-fold, from 7.77 to 30.77%.

Whether the biliary precut was performed before or after 10 attempts at cannulation also significantly changed the postprocedure pancreatitis rate in our study, from 9.68 up to 35.29% – a four-fold difference. The increase was similar to that between less than and more than 10 attempts at cannulation, without precutting (from 7.64 to 28.57%). Adding the precut to persistent cannulation attempts further increased the pancreatitis rate, from 28.57 to 35.29%, although the difference was not statistically significant. These data do not agree with three previous studies [15,17,29] that used the cannulation time instead of the number of attempts and found no difference between delayed precutting and persistence in cannulation.

A biliary precut performed before 10 attempts at cannulation did not significantly raise the pancreatitis risk in comparison with cases in which successful biliary cannulation was achieved with fewer than 10 attempts and without precutting. This confirms that the precut *per se* should not be considered an independent risk factor for postprocedure pancreatitis in experienced hands.

Conclusion

This prospective analysis on a large series of patients undergoing ERCP for bile duct stones showed that a 'needle-knife' precutting to access the biliary ductal system performed before 10 attempts have been made at cannulation did not increase the risk for postprocedure pancreatitis, compared with the standard cannulation technique, and it should be preferred rather than persisting at cannulation when up to nine cannulation attempts have already been made, because the risk for pancreatitis is significantly higher for either repeatedly trying for cannulation or adding a delayed precut.

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Conflicts of interest

There are no conflicts of interest.

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