Needle Knife Sphincterotomy Does Not Increase the Risk of Pancreatitis in Patients With Difficult Biliary Cannulation

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BACKGROUND & AIMS: **Biliary cannulation is unsuccessful during 5%–10% of endoscopic retrograde cholangiopancreatography (ERCP) procedures. Needle knife sphincterotomy (NKS) can improve success of cannulation but is often used as a last resort and is associated with post-ERCP pancreatitis (PEP). We evaluated the safety and efficacy of performing NKS during early stages of difficult cannulation and the relationship between difficult cannulation and the risk of PEP.**

METHODS: **We performed a prospective trial of consecutive patients with an intact papilla who were undergoing ERCP at tertiary referral center; 73 patients were defined as having difficult biliary cannulation according to predefined cannulation parameters. These patients were randomly assigned to groups that received either NKS or continued standard cannulation. Main outcome measures were PEP and successful biliary cannulation.**

RESULTS: **Of 464 patients with an intact papilla undergoing ERCP, 73 met the criteria for difficult cannulation. Cannulation success in difficult cannulation cases was 86%, with a PEP rate of 19%. There was no difference in eventual cannulation success between the groups. However, 65% of the patients assigned to the standard cannulation group required crossover to NKS. There was no significant difference in development of PEP among patients in the early NKS group (20.5%) vs standard cannulation (17.6%). Pancreatic duct stents were inserted in 23 of the patients in the early NKS arm and in 15 in the standard cannulation arm. The number of cannulation attempts (more than 7) increased the risk of PEP ($P < .01$). On the basis of multivariate analysis, independent risk factors for PEP were failure of early cannulation and failure of biliary cannulation.**

CONCLUSIONS: **Early application of NKS during difficult cannulation does not increase the risk of PEP. The risk of PEP increases greatly after 7–8 attempts at or failure of cannulation. Further studies are required to assess whether early implementation of NKS during difficult cannulation reduces the development of PEP. Australia and New Zealand Clinical Trials registry: ANZTRN 12,612,000,060,842.**

Keywords: Precut Sphincterotomy; Liver; Pancreas; Surgery.

Endoscopic retrograde cholangiopancreatography (ERCP) is a pivotal component of the established therapies for pancreaticobiliary disease.[1] Since first reported more than 40 years ago,[2] cannulation of the desired duct remains one of the integral elements to a successful procedure; however, conventional techniques even in high-volume centers fail in 5%–10% cases.[3,4] Needle knife sphincterotomy (NKS), also referred to as precut sphincterotomy or access papillotomy,[5] may allow cannulation success rates to approach 100%. However, it has long been considered technically challenging and potentially hazardous.[6] NKS is often performed at the end of a difficult and prolonged cannulation effort that is associated with repeated attempts and multiple prior pancreatic duct (PD) cannulations. These 2 factors are both independently linked with a higher incidence of post-ERCP pancreatitis (PEP).[7,8] Prospective evaluation of the quantitative relationship between difficult cannulation and PEP is not established; however, as time and failed attempts accumulate, there is a watershed period where the likelihood of selective biliary cannulation declines and the risk of PEP swiftly escalates.[9] The challenge is to identify the seminal events immediately before this point and apply an intervention to reduce the risk and deliver success. The application of an early NKS strategy for difficult cannulation in response to these triggers may reduce the occurrence of PEP; this formed the basis for our study.

Abbreviations used in this paper: CS, continued standard; ERCP, endoscopic retrograde cholangiopancreatography; ES, early success; NKS, needle knife sphincterotomy; OR, odds ratio; PD, pancreatic duct; PEP, post-ERCP pancreatitis.

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Methods

The study was designed as a randomized, prospective single-center study. The Sydney West Area Health Service human ethics and research committee approved the study. All patients gave their informed consent.

Patients

From July 2007–December 2009, all patients with an intact papilla and without exclusion criteria were invited to participate in the study. Exclusion criteria included the following: age younger than 18 years, acute illness (hypoxia, systolic blood pressure less than 90 mm Hg, hemodynamic instability), inability or refusal to give informed consent, and recent (<2 weeks) diagnosis of acute pancreatitis. Patients with a preprocedure diagnosis of pancreatic or ampullary malignancy were excluded, because in our experience, PEP is very uncommon in these subgroups, and tumor-related anatomic variation may alter the cannulation technique. Patients with surgically altered anatomy (Billroth-II, Roux-en-Y anastomosis) were also excluded, because cannulation technique is fundamentally different compared with normal anatomy. As a tertiary referral center, referrals are received from other centers/endoscopists for difficult cannulation cases including previously failed biliary cannulation. Patients with a previously failed cannulation were enrolled in the study unless an NKS had been previously attempted or the patient had developed PEP as a result of the previous attempt.

Study Design

The study was performed in a tertiary referral university hospital endoscopy unit, which has a dedicated ERCP training fellow. Each procedure was supervised by 1 of 4 senior endoscopists (M.J.B., S.J.W., R.H., and D.R.), each with a career experience of more than 3000 ERCPs and an individual annual caseload of between 100 and 600 procedures per year. Procedures were performed in a dedicated endoscopic fluoroscopy room, with the patient in the prone position with monitored anesthesia care by using propofol-based sedation. An Olympus Exera TJF-160R duodenoscope (Olympus Optical, Japan, Tokyo) was used in all cases. All procedures were commenced with a wire-guided cannulation technique that has been previously described in detail,[4] which uses a triple-lumen sphincterotome (CleverCut3; Olympus Optical Co, Ltd) and a 400-mm length hydrophilic wire (Jagwire; Boston Scientific, Natick, MA). If required, an NKS was performed by using a 3-mm-long Olympus needle knife (Olympus Optical Co). The dedicated ERCP fellow commenced the majority of procedures. A strictly defined cannulation protocol was implemented throughout the study: 5 minutes allocated for successful biliary cannulation from the first touch of the papilla, a total of 5 cannulation attempts, and no more than 2 inadvertent PD cannulations. If the fellow exceeded any of the parameters, the consultant took over the case. The consultant also followed the same cannulation protocol. Successful cannulation was defined as free and deep instrumentation of the biliary tree. A cannulation attempt was defined as sustained contact between the sphincterotome and the papilla for at least 5 seconds. Early success (ES) was defined as successful cannulation within the parameters of the cannulation protocol. If the consultant was unsuccessful according to the prescribed parameters, the patient was then randomized to continued standard (CS) cannulation techniques or to early NKS. Randomization was revealed at the time by the opening of a sealed envelope by a member of the endoscopy team. After randomization, 10 minutes was allotted for cannulation with unlimited attempts. At the conclusion of the additional 10 minutes, patients in the standard cannulation arm were classified as conventional cannulation failures. Crossover to the NKS arm was then allowed if clinically appropriate. Time intervals were based on previous prospective correlation trials at our center.[4,9]

The NKS technique was standardized and followed the conventional (freehand papillotomy/deroofing) NKS (Figure 1) method.[4,10] The cut was commenced from the superior aspect of the papillary orifice and extended upward in 2-mm increments by using Endocut I from an ERBE Vio 300 generator (Tübingen, Germany). The goal was to completely divide the majority of the papillary mound in a controlled stepwise fashion with a single pass, thus unroofing the biliary orifice, which once identified was then selectively cannulated with a guidewire passed through a sphincterotome. All operators used the same technique. The sphincterotomy was then completed in the conventional manner after successful cannulation.

Endoscopists placed a pancreatic stent (Zimmon; Cook Medical, Bloomington, IN; single pigtail, 2–5 cm 5F, single proximal flange with the proximal end not beyond the pancreatic genu) before NKS if the PD had been cannulated at least twice. If the

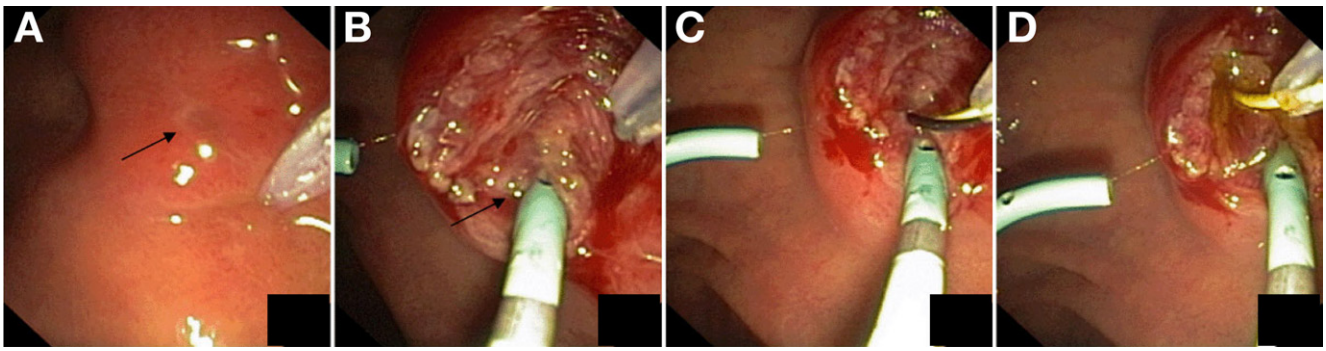

Figure 1. Technique of NKS over PD stent. (*A*) Sphincterotome tip at PD orifice. *Arrowhead* at biliary orifice. (*B*) A 5F pancreatic stent in situ. Papillotomy NKS performed through the fibromuscular sphincter and exposing the biliary orifice (*arrowhead*) between the 10 and 11 o'clock positions in relation to the pancreatic stent. (*C*) Soft-tipped 0.035-mm biliary wire inserted through biliary orifice and into bile duct (confirmed on x-ray not shown). (*D*) After complete sphincterotomy with biliary wire and pancreatic stent still in situ and evidence of spontaneous bile drainage.

Table 1. Excluded Patient Preprocedural Indications

Exclusion indication	Number
Acute pancreatitis	79 (35%)
Pancreatic cancer/mass	61 (27%)
Age <18 y	7
Pancreatic indication	6
Clinical instability	5
No sphincterotomy performed	4
Previous unsuspected sphincterotomy	4
Surgically altered anatomy	4
Ampullary cancer	3

PD had not been cannulated during the attempt(s) of biliary cannulation, then a PD stent was not placed. No medication was used for PEP prophylaxis.

Data collected included patient demographics, indications, findings, and outcome as well as extensive cannulation data including time to cannulation, number of attempts, number of pancreatic cannulations or injections, use of a pancreatic stent, and endotherapy used. A member of the ERCP team recorded cannulation data in real time. Primary outcomes were biliary cannulation success and PEP incidence.

Follow-up

All patients were assessed clinically at the bedside before discharge from the endoscopy unit. Outpatients remained in the unit for 4 hours after the procedure. Patients with significant abdominal pain were admitted for observation. All patients were asked to have serum collected for determination of amylase and lipase levels the day after ERCP. The ERCP fellow performed follow-up telephone interviews on day 1 and day 30 after the procedure. If a PD stent was inserted, patients returned for an abdominal x-ray on day 7; if still present, the stent was retrieved endoscopically within the following 24 hours.

All ERCP complications were defined and graded by using consensus criteria.[11] Pancreatitis was defined as a 3-fold elevation of serum amylase above the upper limit of normal on day 1 after procedure in the setting of typical abdominal pain. In the event of PEP, a gastroenterologist managed all cases, and the data were collected prospectively to grade the severity of the complication.

Randomization

Patients were randomized by using a random number generator, with the allocation sealed in sequentially numbered opaque envelopes. An individual not involved in the trial performed the randomization and concealment in envelopes. The envelopes were opened in sequence when the randomization criteria were reached, so the treating endoscopist was blinded to treatment arm allocation until the envelope was opened by another member of the endoscopy team.

Statistical Analysis

Analysis of the data was performed by using statistical software package SPSS for Windows version 14 (SPSS, Inc, Chicago, IL). Baseline characteristics of all groups were analyzed by using Fisher exact test. Final results for all randomized patients were calculated on an intention-to-treat analysis, in which randomized patients to the standard therapy arm were all analyzed in that arm regardless of whether NKS was used. Statistical significance was judged on the basis of a P value $<.05$ via Pearson χ^2 or Fisher exact test as appropriate. Sample size was calculated for PEP incidence with each arm to have 76 patients; calculation was performed to an 80% power by using the postulation that on the basis of our previous published experience, PEP incidence would reduce from 20% to 5% with early NKS.[9] Interim analysis was scheduled for 3 years after institutional ethics approval.

All authors involved in the study were involved in the analysis and drafting of the manuscript. All contributing authors approved the final manuscript.

Results

Prospective recruitment was performed between July 2007 and November 2009, during which time a total of 2087 ERCP procedures were performed. A total of 690 patients with an intact papilla were referred, and 226 patients were excluded (Table 1), 35% with recent acute pancreatitis and 27% with pancreatic/distal biliary malignancy. Four hundred sixty-four patients met the inclusion criteria (Table 2). The mean age of the study patients was 56 years (range, 18–95); 62.9% of the patients were female. The most common indications were suspected or known biliary calculi (68.8%); suspected sphincter of Oddi dysfunction was the indication in 4.1%. There were no statistically significant differences between any of the groups in relation to procedural indications (Table 2). Nine patients had a previously failed biliary cannulation (which did not include NKS); none had developed PEP subsequent to the previous failed ERCP. The overall cannulation success rate after 1 procedure was 454 of 464 (97.8%). The fellow commenced the procedure in 90.3% of cases (419 of 464).

ES was achieved in 391 patients (84%), 268 (64%) by the fellow alone and the remainder (123) by the consultant. The initially unsuccessful 73 patients were subsequently randomized, 34 for CS therapy and 39 for early NKS technique. Of the 9 patients with a previously failed ERCP, 6 had ES, and 3 required randomization (2 for early NKS and 1 in CS group).

Table 2. Demographic Details and Indications for ERCP According to Treatment Arms

	ES (n = 391)	CS therapy (n = 34)	Early NKS (n = 39)
Mean age ± standard deviation, *y*	55 (19.1)	57 (17.2)	59 (17.6)
Female sex, *%*	63	66	72
Indications			
Known CBD stone, *%*	26.3	17.6	10.3
Suspected CBD stone, *%*	44.5	47.1	51.3
Sphincter of Oddi dysfunction, *%*	3.6	8.8	5.1
Obstructive jaundice, *%*	5.6	5.9	7.7
Nonpancreatic malignancy, *%*	1	0	5.1
Bile leak, *%*	7.4	2.9	10.3
Primary sclerosing cholangitis, *%*	0.3	2.9	0
Dilated bile ducts, *%*	3.1	8.8	5.1
Cholangitis, *%*	7.7	5.9	2.6
Benign biliary stricture, *%*	0.5	0	2.6

CBD, common bile duct.

Table 3. Univariate Analysis of Risk Factors for PEP

	PEP patients (n = 23)	Non-PEP patients (n = 441)	*P* value
Mean age, *y*	59.8	55.7	NS
Male:female	1:1.5	1:1.74	NS
Mean time for cannulation (*min*)	10.4	4.7	<.001
Mean number of attempts	6.7	3.1	<.001
Mean number of PD cannulations	3.4	0.6	<.001
NKS used	11 (48%)	12 (3%)	<.001
Randomized to CS group	6	28	.001
Randomized to early NKS group	8	31	.001
Cannulation failure	6 (10%)	4 (0.9%)	<.001
PD stent	8 (35%)	35 (8%)	.001

Twenty-two of the CS group (64.7%) failed to achieve biliary cannulation after the allotted 10 minutes and were crossed over to needle knife according to the study protocol. Therefore, a total of 61 patients in the study (13.1%) underwent NKS. Cannulation success in the early NKS group was 87% (34 of 39). By intention-to-treat analysis, the overall cannulation success in the CS group was 35.3% (12 of 34) (without crossover to NKS). Success in the crossover group was 77.3% (17 of 22), giving a total success in the CS group of 85.3% (29 of 34). The total success of NKS in the study was therefore 83.6% (NKS arm 34 of 39 + crossover "salvage" group 17 of 22). There was no statistical difference for overall success ($P = 1.0$) between the 2 randomized groups. Mean time to successful deep biliary cannulation after commencing NKS was 322 seconds (range, 90–945 seconds). Patient flow in the study is summarized diagrammatically in Supplementary Figure 1.

Pancreatic stents were inserted in 43 patients (9.3%), 5 in the ES group (1.3%) and 38 in the randomized group (52%) ($P < .01$). There was no significant difference in the use of PD stents between the 2 randomized groups, 15 of 34 (44%) in the CS arm and 23 of 39 (59%) in the NKS arm. Similarly, there was no statistical difference in the use of PD stents in the successful CS group vs those in the CS group who required crossover to NKS, 5 of 12 (41%) vs 10 of 22 (45%).

The overall PEP incidence was 23 of 464 (4.95%, 17 mild and 6 moderate). PEP occurred in 9 of 391 (2.3%) in the ES group compared with 14 of 73 (19%) in those who required randomization ($P < .01$). PEP rates were 6 of 34 (17.6%) and 8 of 39 (20.5%) in the CS and NKS groups, respectively ($P = 1.0$). There was no difference in the severity of pancreatitis between the 2 study arms (3 and 6 mild and 3 and 2 moderate in the CS and NKS arms, respectively). In the CS arm, PEP rates were 3 of 22 (13.6%) with crossover and 3 of 12 (25%) without crossover ($P = .64$). PEP was noted to be significantly higher in patients with PD stent insertion (8 of 43, 18%) compared with those without PD stent (15 of 348, 4%) ($P < .005$).

Significant risk factors for PEP on univariate analysis included time to cannulation, number of cannulation attempts, use of NKS, and use of PD stents (Table 3). On multivariate analysis (Table 4), only 2 variables were significantly associated with PEP development, failure of early cannulation requiring randomization (odds ratio [OR], 8.2) and failure of biliary cannulation (OR, 11.17). Use of NKS (OR, 0.47) and use of a PD stent (OR, 1.67) were not independently associated with PEP. There was no significant difference in PEP incidence relative to procedural indication or the involvement of the fellow during the procedure (20 of 419, 4.95% vs 3 of 45, 6.66%; $P = .9$).

The incidence of PEP was associated with both an increasing number of attempts as well as increasing time to successful cannulation (Figure 2). After 4 attempts the risk of PEP was 3.4%; after 5–6 attempts the risk rose to 5.1% and subsequently rose sharply to a risk of 21% after 9–10 cannulation attempts. Failed cannulation was associated with a PEP incidence of 60% (6 of 10). The development of PEP was significantly associated with more than 8 cannulation attempts and more than 10 minutes for cannulation.

Post-sphincterotomy bleeding occurred in 13 patients overall (2.8%), 10 from the ES group (2.6%), 2 from the CS group (8.3%), and 1 from the NKS group (2.6%). Seven patients required repeat endoscopy for bleeding; all were successfully treated with either adrenaline injection (4) or endoscopic clipping (3). There were no perforations or deaths in the study population.

Discussion

Despite the widespread and longstanding practice of ERCP, there remain 2 unresolved problems, failure of biliary cannulation and PEP. NKS is a valuable method to achieve biliary access when conventional techniques have failed; however, the technique has long been associated with higher rates of PEP.[12] In this prospective study we have demonstrated that difficult cannulation leads to a higher PEP rate compared with early successful cannulation, and that NKS is not in itself directly associated with PEP development.

A retrospective analysis[9] of prospectively collected comprehensive cannulation data in 732 intact papilla ERCPs from our group has detailed the linear association between the number of cannulation attempts and the rate of PEP. In that study, NKS was not associated with PEP on both univariate and multivariate analysis. The current study, which was specifically designed to prospectively analyze NKS and difficult cannulation, confirms the lack of an independent association of NKS with PEP and quantifies the direct relationship between difficult cannulation and PEP development. PEP risk is significantly increased by more than 8 cannulation attempts and cannulation time greater than 10 minutes. Therefore, this study further confirms the hypothesis that PEP is related to difficult cannulation and that the use of NKS is a surrogate marker for difficult cannulation. Importantly, failed cannulation, reflecting persistent and repeated attempts, was associated with the greatest OR for PEP development. Furthermore, it is interesting to speculate that division of the biliary sphincter after successful cannulation

Table 4. Multivariate Analysis of Risk Factors for PEP

	OR	95% confidence interval	Significance
Unsuccessful early cannulation and required randomization	8.2	0.99–67.3	.05
Cannulation failure	11.17	1.80–69.5	.01
NKS use	0.47	0.09–2.32	.36
PD stent	1.67	0.47–5.90	.43

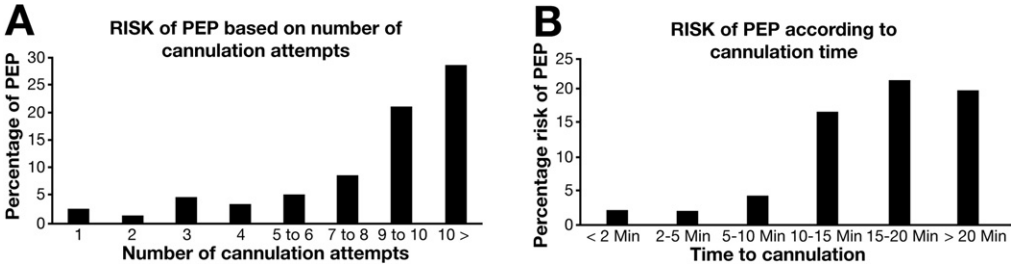

Figure 2. (*A*) Risk of PEP based on number of cannulation attempts. (*B*) Risk of PEP based on cannulation time.

(as was the norm in this cohort) further mitigates against PEP occurrence or severity by facilitating PD drainage.

Consensus on the definition of difficult biliary cannulation is yet to be reached. Such a definition should take into account the number of attempts on the papilla, the time elapsed from the first attempt, and the number of PD cannulations and/or contrast opacifications.[13] By using the definition used in this study (10 attempts, 10 minutes, or 4 PD cannulations), 16% of patients had clearly defined difficult cannulation. As evidenced in this study, these patients have entered a higher bracket of PEP risk (OR, 8.2); a change in cannulation strategy is required, and efforts to mitigate PEP development should be considered including pancreatic stent placement or rectal nonsteroidal anti-inflammatory drug suppository.[14]

The relationship between the use of NKS in difficult cannulation and the development of PEP has been prospectively evaluated in 3 previously published studies.[15–17] In keeping with the findings of the current study, all previous studies have demonstrated the lack of an independent association between NKS and PEP. There are, however, important differences between the current study and those previously published. None of the previous studies were performed with an initial wire-guided cannulation protocol, and none incorporated the use of pancreatic stents; both techniques now are increasingly recommended to avoid PEP.[18,19] In addition, none of the previous studies contained a predetermined definition of difficult cannulation that included number of cannulation attempts, despite its now proven critical importance in quantifying risk for PEP and difficulty of cannulation. Only one of the studies had a comparison group of easy cannulation that allowed ascertainment of the background PEP incidence.[15] Only this study had fellow involvement; however, this study did not have a strictly defined follow-up protocol or routine pancreatic enzyme assays. The study by Cennamo et al[17] excluded mild severity pancreatitis as a complication, thus greatly reducing the overall complication rate and limiting the ability to extrapolate from this study. Excluding mild PEP from our study shows similar results (overall PEP 1.3%, 6.6% PEP associated with NKS).

The method of NKS in the current study was uniformly the deroofing technique, cutting from the papillary orifice upward (Figure 1). No method of NKS has been shown to be superior over other NKS techniques.[20,21] All the endoscopists in the study were experienced in the NKS technique, and no statistical differences in success rates or complications were observed among the individual endoscopists. The NKS technique remains an advanced therapeutic procedure with a significant learning curve,[22] and as such, it should only be performed by appropriately trained or adequately supervised endoscopists.[23] However, this study further underlines the importance of NKS to achieve successful biliary cannulation because it was used in 13.1% of the entire study cohort including almost two-thirds of patients who had unsuccessful biliary cannulation after 20 minutes of standard cannulation techniques.

Pancreatic stents were used in 9% of all patients, including 52% of the randomized groups. Pancreatic stents were only used in those patients in whom pancreatic instrumentation had occurred during attempts at cannulation. Pancreatic stents have been shown to be effective to reduce the incidence and severity of PEP in high-risk indications.[24,25] Because difficult cannulation was shown to be an independent PEP risk factor on multivariate analysis (OR, 8.2) in this study, difficult cannulation should be considered to be another indication for pancreatic stenting. Another reason to consider the use of PD stent in difficult cannulation is that it can be used to protect the pancreatic orifice during NKS and to facilitate biliary localization after NKS (Figure 1*B* and *C*).[10]

Although the study arises from a single tertiary referral academic center, we believe that the results may be applicable outside this setting when performed by experienced biliary endoscopists. More than two-thirds of the procedural indications were for biliary stone disease. An endoscopy fellow commenced the procedure in more than 90% of cases, and the consultants involved had a variable annual work load of between 100 and 600 cases per year. Importantly, no difference in PEP rates was noted among individual endoscopists stratified for number of cases per year. Advances in endoscopic imaging technology in the last few years mean that NKS can currently be performed with greater precision than in previous eras. After deroofing/dividing the papilla, it is now usually possible to carefully dissect out and accurately localize the biliary orifice, which is then selectively cannulated.[10]

This study has several limitations. The study was terminated at scheduled interim analysis because of slower than anticipated recruitment and evidence that superiority of NKS over CS would not be proved with further enrollment; at study conclusion, approximately half of the calculated sample size for each randomized group were enrolled. The initial model for calculation of sample size was, in retrospect, underpowered because of overestimating the likely benefit of an early NKS strategy in cases of difficult cannulation. Potential reasons for this overestimate include (1) the protocol allowed crossover from CS to NKS (65% of CS cases), potentially altering PEP rates, and (2) the exclusion of cases of pancreatic malignancy. On the basis of our prior experience,[9] to not allow crossover to NKS would have increased overall failure rates and would have been detrimental to patient outcome and thus unethical. The exclusion of pancreatic malignancy indications is a potential factor because it is widely accepted that these patients have a lower pancreatitis rate. This group comprised a significant component of previous

NKS studies,[15–17] and the exclusion of this low-risk group may have artificially inflated the PEP incidence.

Although this study fails to prove the primary aim, namely that early NKS is superior to persistent attempts in preventing PEP in difficult cannulation, we believe that there are important conclusions that can be drawn from this study. Most importantly, we have demonstrated and defined prospectively the technical parameters that can be used to identify the transition to a high-risk PEP environment. Understanding the technical aspects of difficult cannulation may allow further research into additional measures to prevent PEP, such as nonsteroidal anti-inflammatory drug suppository.[26]

On the basis of the findings of this study, along with other published literature, we propose the following approach in cases of difficult biliary cannulation. After 6–7 dedicated attempts without success, a decision should be made on whether to proceed with additional attempts via a second tier of techniques/alternative cannulation strategy or to cease the procedure. At this point the risk of PEP is steadily escalating with each attempt. This decision should be made on the basis of the procedure indication and risk profile of the patient, the skill and expertise of the endoscopist and their team, the availability of medical resources in the event of complications, as well as alternative methods of biliary access including tertiary referral[27,28] or interventional radiology.[29] The current data confirm that NKS is a safe and effective strategy when used by experienced biliary endoscopists and does not increase the risk of PEP. However, the early implementation of NKS to prevent the occurrence or ameliorate the severity of PEP in difficult cannulation has not yet been proved. Other strategies for difficult cannulation may yet include wire cannulation after pancreatic wire[30] or stent placement,[31] but at present their role and place in a sequential protocol that may include early NKS require further large-scale prospective multicenter study.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2012.12.017.

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Reprint requests

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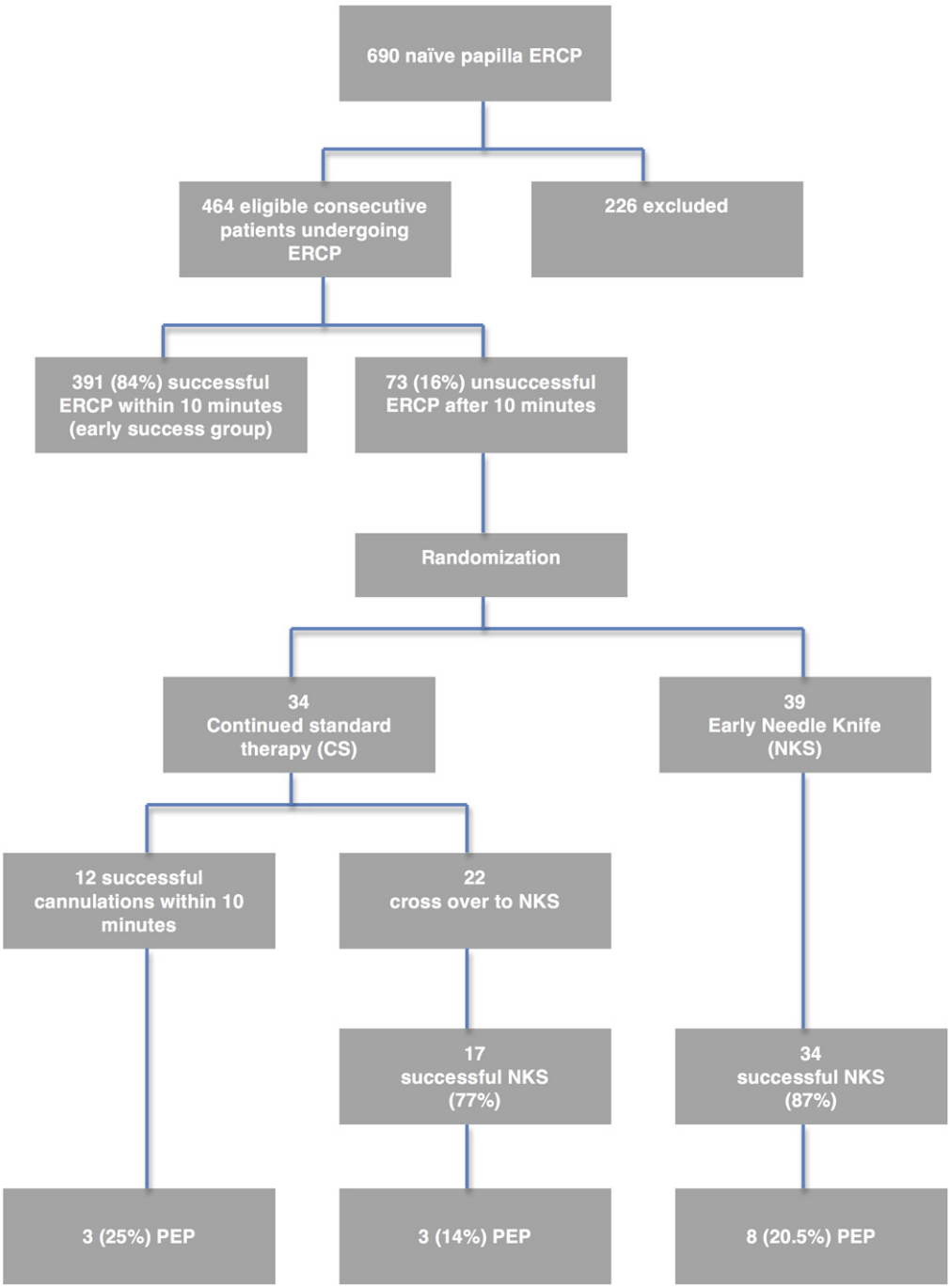
Conflicts of interest

The authors disclose no conflicts.



Supplementary Figure 1. Flow diagram of the patient outcome.