

## Is the Isolated-Tip Needle-Knife Precut as Effective as Conventional Precut Fistulotomy in Difficult Biliary Cannulation?

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**Background/Aims:** Needle-knife precut fistulotomy (NK-F) is a well-known freehand technique for difficult biliary cannulation (DBC). Another approach involves the use of Iso-Tome<sup>®</sup>, a modified precutting device with an insulated needle tip to prevent direct thermal injury. This comparative study aimed to evaluate the efficacy of the Iso-Tome<sup>®</sup> precut (IT-P) compared to that of NK-F for DBC. **Methods:** Patients with a naïve papilla who underwent early IT-P or NK-F for DBC were enrolled. DBC was defined as failure to achieve selective biliary access by wire-guided cannulation despite 5 minutes of attempted cannulation,  $\geq 5$  papillary contacts, or a hook-nose-shaped papilla. The primary endpoint was the primary technical success rate, which was based on a noninferiority model. **Results:** A total of 239 DBC cases were enrolled. The primary technical success rates were 74.7% (89/119) in the IT-P group and 91.6% (110/120) in the NK-F group (lower limit of 90% confidence interval,  $-0.23$ ;  $p=0.927$  for a noninferiority margin of 10%). The total technical success rates were 87.4% and 95.0%, respectively ( $p=0.038$ ). The mean precutting times for successful biliary access were 11.2 minutes for IT-P and 7.3 minutes for NK-F ( $p<0.01$ ). The procedure-related adverse event rates were 9.2% for IT-P and 5.8% for NK-F ( $p=0.318$ ). The rates of post-endoscopic retrograde cholangiopancreatography pancreatitis were 4.2% and 2.5%, respectively ( $p=0.499$ ). **Conclusions:** IT-P failed to exhibit noninferiority compared with NK-F regarding the primary technical success rate of DBC, but there was no difference in the frequency of adverse events. (*Gut Liver* 2018;12:597-605)

**Key Words:** Cannulation; Biliary; Precut; Iso-Tome; Needle-knife

## INTRODUCTION

Despite the various endoscopic techniques available to facilitate selective biliary access, selective biliary cannulation may be incomplete in up to 18% of patients, although this falls to  $\leq 5\%$  in experienced hands.<sup>1,2</sup> Therefore, various endoscopic techniques, such as guidewire-assisted cannulation, double guidewire-induced cannulation, precut papillotomy, or transpancreatic sphincterotomy with or without placement of a pancreatic stent, have been used to improve cannulation success rates.<sup>3-9</sup> Among them, precut sphincterotomy as a rescue method was first introduced by Siegel in 1980.<sup>8</sup>

Initial reports warned of the risk of complications such as post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, and recommended that precut sphincterotomy should be performed only by experienced endoscopists. However, the prolonged procedure time for cannulation, the excessive manipulation causing ampullary edema and injury, and repeated unintentional pancreatic duct (PD) cannulation before the trial of the precut itself have been shown to be independently associated with increased risks of post-ERCP pancreatitis (PEP).<sup>3,4,10-12</sup> Meta-analyses of precut sphincterotomy and conventional cannulation attempts in patients with difficult biliary cannulation (DBC) stated that the rate of PEP was lower with the precut technique, while those of successful biliary cannulation and complications did not differ.<sup>4</sup> Currently, precut fistulotomy using needle-knife (NK) is the preferred technique in DBC by an experienced endoscopist.

Especially regarding precut fistulotomy, it may not contact the main PD directly, and does not significantly increase the severity of pancreatitis. Early institution of precut in DBC can improve the successful cannulation rate without increasing the

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frequency of complications, such as PEP. Indeed, one recent report showed that NK-precut fistulotomy (NK-F) might also be feasible and safe as an initial procedure for biliary access in patients with choledocholithiasis who are at high risk of PEP.<sup>13</sup>

Another precut tool, the NK papillotome, Iso-Tome<sup>®</sup> (MTW Endoskopie, Wesel, Germany), has an isolated, semi-oval-shaped tip to reduce direct electric or thermal damage caused by the tip of the incising needle.<sup>14</sup> This modification might facilitate its use and reduce direct thermal and electrical injury, as well as direct mechanical trauma to the PD by controlling the depth of needle penetration during incision.

Our group previously reported the technical feasibility of Iso-Tome<sup>®</sup> precut (IT-P) in failed primary biliary cannulation, but the technical feasibility of a single-armed approach or retrospective results from a single user have been described.<sup>14-16</sup> Therefore, this prospective comparative study evaluated the technical feasibility and procedure-related adverse event rates of IT-P compared with traditional precut fistulotomy using a conventional NK regarding DBC.

## MATERIALS AND METHODS

### 1. Study design and main outcomes

This study was performed as a single-center, prospective, randomized, noninferiority trial. The primary endpoint was the primary technical success rate of IT-P and NK-F for selective biliary access regarding the DBC; that is, an initial wire-guided cannulation time  $\geq 5$  minutes,  $\geq 5$  papillary contacts, or a hook-nose-shaped papilla. The secondary endpoints were procedure-related adverse events and overall procedure outcomes. Randomization was performed by assigning patients according to a computer-generated random number list with a 1:1 allocation, using a random block size of four, by a contributing statistical physician. When the patients meet the DBC criteria, open the random number list by assisting nurse and randomized IT-P or NK-F group. We obtained informed consent prior to ERCP from all patients. This study was performed following confirmation of Institutional Review Board approval. The protocol has been registered in the Clinical Trial Registration database (<http://www.cris.nih.gov/KCT0001960>), and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

### 2. Patients

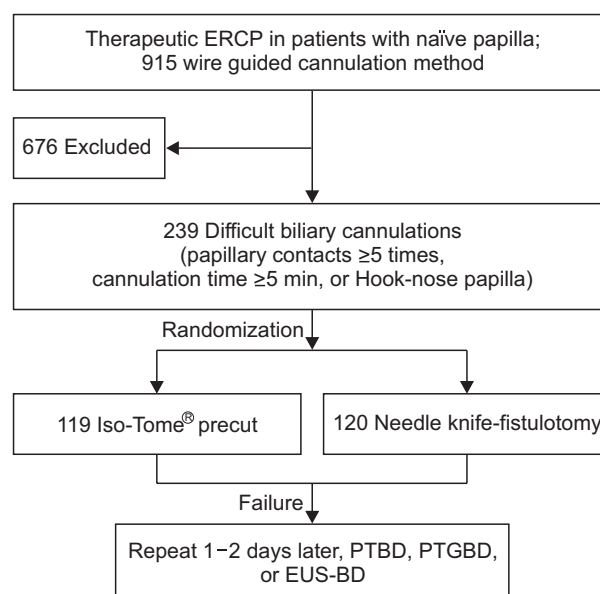
Patients with a naïve papilla who needed therapeutic ERCP were enrolled in a tertiary referral center between November 2015 and December 2016. Therapeutic ERCP was defined by abdominal ultrasonography, computed tomography, or magnetic resonance imaging (or magnetic resonance cholangiopancreatography) with or without endoscopic ultrasonography (EUS). Patients initially planned to undergo diagnostic ERCP were not enrolled in this study. The inclusion criteria were as follows: (1) failed conventional biliary cannulation according to the DBC

criteria (see definition); (2) no serious or uncontrolled medical illness; and (3) provision of informed consent. Exclusion criteria included patient age  $< 18$  years, uncorrectable coagulopathy, history of allergy to radiocontrast agents, inaccessible papilla, surgically altered anatomy, and refusal to participate in the study. Patients with  $\geq 3$  unintentional PD cannulations were also not included according to the inclusion criteria and suggested procedure algorithm (Fig. 1).

### 3. Endoscopic techniques

All patients underwent ERCP (TJF-240 or 260V; Olympus Optical Co., Ltd., Tokyo, Japan) in the left lateral decubitus or prone position after endoscopic sedation. Patients were sedated using a balanced propofol sedation: initial intravenous administration of midazolam (0.05 mg/kg body weight; 1 mg if age  $\geq 70$  years or American Society of Anesthesiologists (ASA) class III-IV) and fentanyl (12.5 to 50  $\mu$ g), followed by repeated doses of 10 to 20 mg of propofol with maintenance of sedation with repeated doses of 10 to 20 mg of propofol to achieve a moderate level of sedation, or midazolam and fentanyl-based sedation at identical doses. Prophylactic antibiotics or analgesics were permitted. A nonsteroidal anti-inflammatory drug suppository for the prevention of PEP was not used in this study because it is not available in domestic. Carbon dioxide insufflation was employed during the endoscopic procedures. The VIO 300D electro-surgical generator (Erbe, Tübingen, Germany) was used for electrocurrent (cutting mode: ENDOCUT, effect 2 or 3, cut duration 2, and interval 3).

Initially, all selective cannulation of the common bile duct



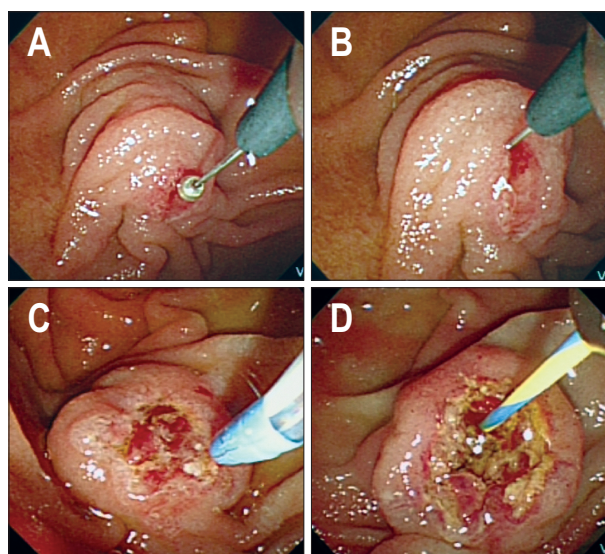
**Fig. 1.** Flow diagram of the study.

ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; PTGBD, percutaneous transhepatic gallbladder drainage; EUS-BD, endoscopic ultrasound-guided biliary drainage.

(CBD) was attempted using a standard wire-assisted biliary cannulation technique. A hydrophilic-tipped Hydra Jagwire (Boston Scientific, Natick, MA, USA) or Tracer Metro (Cook Medical, Winston-Salem, NC, USA), 0.035 inches in a diameter, was preloaded into a pull-type papillotome (flow cut, Olympus Optical; DASH<sup>®</sup> sphincterotome, Cook Medical). The papillotome was oriented from the 11 o'clock to the 12 o'clock position on the major papilla and bowed to align correctly with the axis of the bile duct. Following minimal insertion of the pull-type papillotome into the major papilla, the guidewire was carefully advanced through the CBD under fluoroscopic guidance until it was observed to enter the bile duct. If the PD was entered, the guidewire was simply withdrawn and redirection toward the CBD was attempted.

### 1) Iso-Tome<sup>®</sup> precut

The insulated tip of the Iso-Tome<sup>®</sup> was placed in the orifice of the ampulla of Vater (AV), and tension was applied to the cephalad rim when selective access to the CBD failed according to the DBC criteria. During application of electrocurrent, the Iso-Tome<sup>®</sup> was intentionally pulled further toward the papillary roof at the 11 to 12 o'clock position to avoid direct contact with the orifice of the main PD. Stepwise precutting was repeated until pinkish bile duct mucosa was clearly identified. Then, selective biliary cannulation was attempted using a guidewire technique (Fig. 2). After selective biliary cannulation was suc-



**Fig. 2.** Endoscopic Iso-Tome<sup>®</sup> precut technique. (A) Duodenoscopy showed a prominent ampulla of Vater (AV) with erythema due to primary cannulation failure. The Iso-Tome<sup>®</sup> was introduced at the orifice to perform the precut. (B) The isolated tip of the Iso-Tome<sup>®</sup> was placed at the orifice of the AV, and then precutting was performed with slight upward tension in the 11 to 12 o'clock direction. (C) Following successful precut, the intrapapillary mucosa was noted, and conventional guidewire cannulation was attempted. (D) Successful wire-guided bile duct cannulation using a papillotome was achieved.

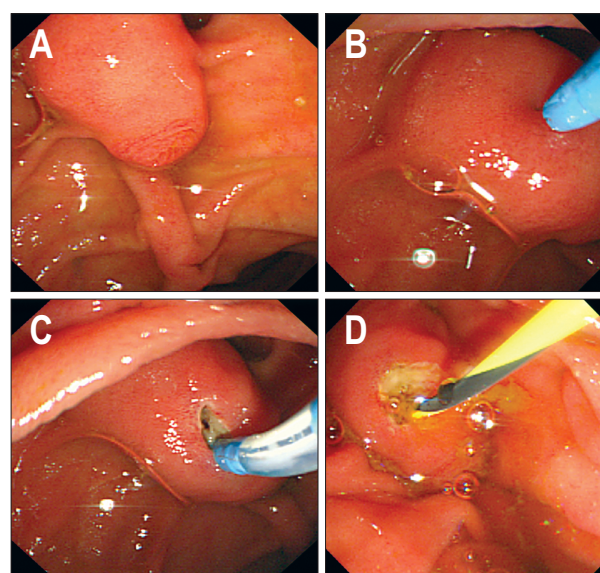
cessfully achieved, an extended endoscopic sphincterotomy was performed using a standard pull-type papillotome, NK (extended endoscopic sphincterotomy, extended EST) or endoscopic transpapillary pneumatic balloon dilation (EPBD), according to the therapeutic purpose.<sup>14-16</sup>

### 2) Needle-knife precut fistulotomy

An NK-F (Microtome; Boston Scientific) was also performed as an early rescue technique when selective access to the CBD failed according to the DBC criteria. Fistulotomy was initiated over the maximal bulging portion of the AV and then extended upwards or downwards little by little. However, the incision stopped short of the papillary orifice or papillary roof to prevent duodenal perforation (Fig. 3). After the incision into the intraduodenal segment of the CBD, when bile trickled out from the incision site, the bile duct was negotiated using a guidewire-preloaded NK. An additional extended EST by NK or EPBD was also performed according to the therapeutic purpose.<sup>17</sup>

In this study, PD stent placement to enhance primary biliary access or routine prophylactic placement to prevent PEP was not planned. However, in cases of difficult precutting with unintentional PD cannulation ( $\leq 2$  times) during selective biliary cannulation, a PD stent was placed during the endoscopic procedure. A PD stent was also considered in cases of a difficult precut, based on the decision of the endoscopists. A 5 F, single-pigtail pancreatic stent (Cook Medical) was used in these cases.

When selective biliary cannulation failed in both IT-P and NK-P, we attempted the second trial using the same method



**Fig. 3.** Endoscopic conventional needle-knife (NK)-fistulotomy technique. (A) Duodenoscopy showed a bulging ampulla of Vater (AV). (B) NK incision started at the maximal bulging point of the papillary roof of the AV. (C) Following small incremental incisions in the papillary roof, guidewire insertion was attempted using NK. (D) Successful bile duct cannulation was achieved.

1 or 2 days later. If urgent drainage was needed in cases with sepsis, subsequent percutaneous transhepatic biliary drainage (PTBD), percutaneous transhepatic gallbladder drainage (PTGBD), or EUS-guided biliary drainage was scheduled on the same day. All endoscopic procedures were performed by two experienced endoscopists with at least 10 and 5 years of experience using the Iso-Tome<sup>®</sup>, and more than 13 and 8 years of experience with NK-precut. Trainees were not involved in this study.

#### 4. Definitions

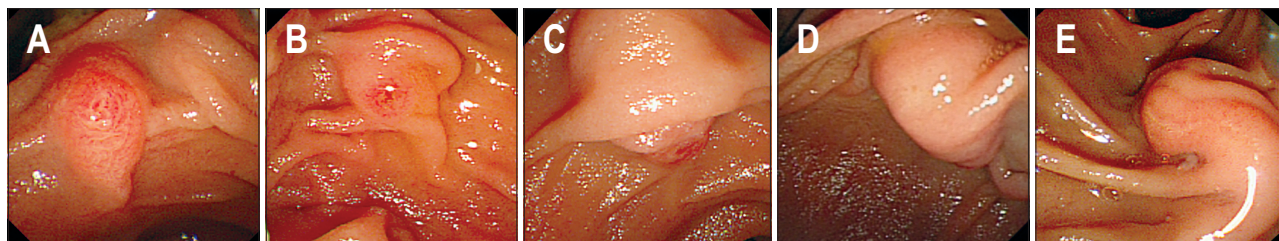
The DBC criteria were defined based on the previous studies,<sup>3,10,11,18</sup> failure to achieve selective biliary access by wire-guided cannulation despite 5 minutes of attempted cannulation after duodenal intubation (cannulation time  $\geq 5$  minutes), five or more papillary contacts, or a hook-nose-shaped papilla. Meaningful papillary contact was defined as sustained contact of the guidewire-preloaded papillotome with the AV for at least 3 to 5 seconds of manipulation.<sup>10,11,19,20</sup> As a difficult criteria, the configuration of a hook-nose-shaped papilla was included based on previous reports (Fig. 4).<sup>10,11</sup> Conventional access with a wire-assisted papillotome may be difficult in hook-nose type papilla because the AV orifice is located at the far distal lower side much like the nostrils of a hooknose. In cases with three, or more than three unintentional PD cannulations, an NK precut from the orifice of the AV was performed following placement of a prophylactic PD stent according to the algorithm. Patients with PD stent-assisted selective biliary access were not included in this study according to the protocol (Fig. 1).

Primary technical success was defined as an intended initial technical success by IT-P or NK-P. Total technical success included primary and secondary technical success. Secondary technical success was defined as a retriel using the same method 1 or 2 days later when primary selective biliary cannulation failed in either IT-P or NK-P. Endoscopic therapeutic success is any type of procedure outcomes such as insertion of biliary stent or removal of stones after selective biliary access. Cannulation time was calculated as the time elapsed between duodenal intubation and initiation of precut. The precut time was the interval between initiation of precut and either successful

biliary cannulation or termination of the procedure on the video monitoring system. Total procedure time was from initiation of precut to completion of endoscopic procedures. Post-ERCP adverse events including pancreatitis were classified according to consensus guidelines.<sup>21</sup>

#### 5. Statistical analysis

The primary outcome analysis was a noninferiority comparison of IT-P and NK-F regarding primary technical success rates on an intention-to-treat principle. From our two reported pooled analysis studies of NK-F, we assumed that the primary technical success rate for NK-F was 93.7%.<sup>10,11</sup> We set a margin of noninferiority for a technical success rate of 10% (this noninferiority margin of 10% would be clinically relevant) according to the results of a pooled analysis and after discussion with the contributing physician. Calculation of the sample size was based on a margin of noninferiority for a technical success rate of 0.1. To achieve a statistical power of 80% with the assumption of a type I error rate of 5%, a total of 222 patients (111 per group) was calculated. Assuming a 5% drop-out rate, we calculated a final sample size of 234 patients (117 per group). Sample size and power were calculated using the PASS version 12 software (NCSS, Kaysville, UT, USA). The noninferiority hypothesis for the primary outcome was assessed using the Z-test with the lower limit of a 90% confidence interval (CI) in the technical success rate and margin of noninferiority. The 90% CI of this difference was reported because one-sided 5% significance was used for the sample size calculation. In our study, a two-sided 90% CI, which corresponds to a one-sided significance level of 0.05, was used for the primary outcome.<sup>22</sup> The characteristics of the study groups were compared using a t-test or Mann-Whitney test for continuous variables and chi-squared or Fisher exact test for categorical variables. A probability level of  $p < 0.05$  was considered to indicate statistical significance. All analyses were performed using STATA version 13.1 (Stata Corp., College Station, TX, USA).



**Fig. 4.** Various ampulla of Vater (AV) configurations. (A) Non-prominent type: a small papilla without marked oral protrusion of the papillary roof. (B) Prominent type: more prominent elevation of the papillary roof. (C) Bulging type: marked swelling from the bulge in the papillary roof to the oral ridge of the duodenal wall. (D) Hook-nose type: a huge bulging type with an invisible AV orifice due to a hook-nose-shaped protrusion. (E) Distorted type: AV of unusual shape and distorted position due to tumor invasion or compression.

## RESULTS

### 1. Analyses of baseline characteristics

A total of 915 patients underwent therapeutic ERCP during the study period. Among them, 676 patients were excluded for the following reasons: successful selective biliary cannulation (n=597), uncontrolled coagulopathy (n=3), surgically altered anatomy (n=5), duodenal obstruction (n=5), and patients who underwent precut following placement of a PD stent due to more than three unintentional PD cannulation (n=66). Finally, a total of 239 primary cannulation failure patients with a naïve papilla (119 IT-P and 120 NK-P) were enrolled and randomized according to strict DBC criteria (Fig. 1). Baseline characteristics did not differ between the two groups. The indications for ERCP did not differ between the two groups. The most common indication for ERCP was choledocholithiasis (62.2% in the IT-P group vs 62.5% in the NK-F group). The configuration of the AV also did not differ between the two groups. Non-prominent, prominent, and bulging-type AVs were the most common types in both groups. A hook-nose-shape was evident in 22 patients (18.5%) in the IT-P group, and 17 patients (14.2%) in the NK-P group (Table 1).

### 2. Primary outcome analysis

The primary technical success rates for selective biliary cannulation were 74.7% (89/119) in the IT-P group and 91.6% (110/120) in the NK-F group (lower limit of 90% CI, -23%;

p=0.927, for a noninferiority margin of 10%). The difference was not significant, and the 90% CI was below the noninferiority margin. The total technical success rates, including secondary success, were 87.4% (104/119) and 95.0% (114/120), respectively (p=0.038). The total technical success rate in the IT-P group was also lower than the NK-F group (Table 2). The cannulation time before initiation of precut did not differ between the two groups. The mean precut times from initiation of precut to successful biliary access were 11.26 minutes in the IT-P group and 7.31 minutes in the NK-F group, respectively (p<0.01) (Table 3).

### 3. The reasons for precut, primary cannulation failure, and management

The most common cause of precut was  $\geq 5$  papillary contacts in both groups (61.3% and 63.3%). The primary causes of selective biliary cannulation failure were a non-prominent AV, improper targeting, distortion or bulging of AV due to tumor invasion, an overhanging circular mucosal fold, and paradoxical reaction in the IT-P group. In the NK-PF group, a non-prominent AV, improper targeting, and distortion or bulging of the AV due to tumor invasion were the principal causes. Cases of secondary cannulation failure in the IT-P group underwent PTBD with maintenance of external drainage (n=1), PTBD with the rendezvous method (n=7), PTGBD (n=2), and surgery (n=2). The remaining three patients were managed conservatively due to their refusal to undergo second endoscopic or interventional procedures. The patients who underwent PTGBD received in-

**Table 1.** Baseline Characteristics

Characteristic	IT-P (n=119)	NK-F (n=120)	p-value
Age, yr	62.93±16.16	66.03±14.68	0.123
Sex, M/F	58/61	53/67	-
Diagnosis			0.181
Choledocholithiasis	74 (62.2)	75 (62.5)	
Gallbladder stone/cholecystitis	4 (3.4)	7 (5.8)	
Malignant biliary obstruction	23 (19.3)	25 (20.8)	
Gallstone pancreatitis	14 (11.8)	10 (8.3)	
Biliary stricture	1 (0.8)	0	
Bile leak	0	2 (1.7)	
Choledochocele	1 (0.8)	1 (0.8)	
Suspected SOD	2 (1.7)	0	
Use of anticoagulation or antiplatelet drugs	18 (15.1)	14 (11.7)	0.076
Papilla configuration			0.718
Non-prominent	30 (25.2)	34 (28.3)	
Prominent	30 (25.2)	30 (25.0)	
Bulging	32 (26.9)	30 (25.0)	
Distorted	5 (4.2)	9 (7.5)	
Hook-nose shape	22 (18.5)	17 (14.2)	

Data are presented as mean±SD or number (%).

IT-P, Iso-Tome® precut; NK-F, needle-knife precut fistulotomy; M, male; F, female; SOD, sphincter of Oddi dysfunction.

terval cholecystectomy. Patients in the NK-F group underwent PTBD with maintenance of external drainage (n=1), PTBD with the rendezvous technique (n=2), EUS-guided biliary drainage (n=2), and surgery (n=1) (Table 4).

#### 4. Therapeutic procedure outcomes and adverse events

Regarding therapeutic procedure outcomes, the final endoscopic therapeutic success rates (including the endoscopic success after radiologic interventions such as PTBD or PTGBD) were 93.3% in the IT-P group and 98.3% in the NK-F group, respectively (p=0.059). The total procedure times were 31.20 and 23.74 minutes, respectively (p<0.01). The prevalence rates of extended EST or EPBD were similar in the two groups. Fifteen patients (12.6%) in the IT-P group and 24 patients (20.0%) in the NK-F group underwent PD stent placement (p=0.122). Among them, 13 patients (10.9%) in the IT-P group and 23 patients (19.2%) in the NK-F group experienced at least one unintentional pancreatic guidewire cannulation (Table 3).

Regarding procedure-related adverse events, PEP developed

in five patients (three mild and two moderate) in the IT-P group and three patients (all mild) in the NK-F group (p=0.499). No severe PEP developed in either group. One case of periampullary microperforation was detected in the IT-P group and was managed conservatively without additional serious complications. No other serious complications or mortality occurred (Table 3).

## DISCUSSION

Previously, the most popular techniques for precut sphincterotomy were cutting upward from the papilla orifice or downward toward the orifice. Incising above the papilla, on its roof, without touching the orifice was not commonly performed. However, NK-F is now considered the preferred free-hand technique for selective biliary access in DBC to improve successful cannulation rates without increasing the frequency of complications, such as pancreatitis.<sup>4,8-11,23-30</sup>

Besides the well-known NK, the Iso-Tome<sup>®</sup> was developed to decrease the frequency of PEP and enhance selective biliary

**Table 2.** Technical Success Rates of Selective Biliary Cannulation Using IT-P and NK-F

No. (%)	IT-P	NK-F	Difference between IT-P and NK-F (90% CI)	p-value
Primary technical success	89/119 (74.7)	110/120 (91.6)	-0.17 (-0.23 to -0.11)	0.927*
Total technical success	104/119 (87.4)	114/120 (95.0)		0.038 <sup>†</sup>

IT-P, Iso-Tome<sup>®</sup> precut; NK-F, needle-knife precut fistulotomy; CI, confidence interval.

\*Noninferiority was defined as a lower limit of 90% CI greater than -10; <sup>†</sup>Pearson chi-square test.

**Table 3.** Overall Procedure Outcomes and Adverse Events

	IT-P (n=119)	NK-F (n=120)	p-value
Cannulation time till precut, min	4.63±1.96	4.88±2.28	0.369
Precut time, min	11.26±8.11	7.31±6.88	<0.01
Procedure time, min	31.20±15.29	23.74±11.62	<0.01
Overall endoscopic therapeutic success*	111 (93.3)	118 (98.3)	0.059
Therapeutic procedures			
Extended EST	30 (25.2)	27 (22.5)	0.623
EPBD	64 (53.8)	59 (49.2)	0.475
Biliary stent	24 (20.2)	35 (29.2)	0.196
Metal/plastic	4 (3.4)/20 (16.8)	9 (7.5)/26 (21.7)	-
Pancreatic stent placement	15 (12.6)	24 (20.0)	0.122
Unintentional PD cannulation ≤2 times	13 (10.9)	23 (19.2)	0.075
Adverse events			
Pancreatitis	5 (4.2)	3 (2.5) <sup>†</sup>	0.499
Bleeding	3 (2.5)	5 (4.2) <sup>†</sup>	0.722
Cholangitis	2 (1.7)	1 (0.8)	0.622
Perforation	1 (0.8)	0	0.498

Data are presented as mean±SD or number (%).

IT-P, Iso-Tome<sup>®</sup> precut; NK-F, needle-knife precut fistulotomy; EST, endoscopic sphincterotomy; EPBD, endoscopic transpapillary balloon dilation; PD, pancreatic duct.

\*Included primary and secondary endoscopic procedures; <sup>†</sup>In the NK-F group, two cases of pancreatitis with bleeding occurred.

access. Theoretically, IT-P is available as a primary classical pre-cut method from the orifice of AV in an upward direction, but without direct PD injury by an insulated needle tip. Although the clinical outcomes and technique of IT-P were reported, these studies were conducted as a retrospective single-arm.<sup>14-16</sup> In the first comparative study of the insulated tip papillotome and classic pre-cut sphincterotomy, the technical success and complication rates were similar.<sup>31</sup> However, technically the initial cannulation method was not standardized. A pull-type sphincterotome with or without guidewire assistance was used. Also, there was no consideration of unintentional PD cannulation. Moreover, pre-cut fistulotomy is preferred over the classic pre-cut sphincterotomy.

In presented noninferiority trial, we used wire-assisted cannulation only as an initial cannulation method. We also applied strict biliary cannulation criteria and difficult AV configuration as a definition of DBC to compare the efficacy of IT-P and NK-F. Frequent unintentional PD cannulation ( $\geq 3$  times) was excluded from this comparison because prophylactic PD stent-assisted pre-cut or cannulation was effective and safe regarding reducing the severity of PEP. The results showed that the primary technical success rate of IT-P was not comparable to that of traditional NK-F. Also, pre-cut time till successful biliary access or termination, and total procedure time were greater in the IT-P group than in the NK-F group. In patients who underwent IT-P, following successful incision, an additional conventional

sphincterotome or papillotome was required for selective biliary access or extension of the incision site for subsequent procedures. Because the IT-P does not have a working channel for a guidewire, and repeated step-wise IT-P and use of a sphincterotome or papillotome are required for successful biliary access. This might result in prolonged pre-cut and procedure times with IT-P. However, there was no difference in the frequency of procedure-related adverse events. IT-P in cases of DBC was also safe and not associated with a higher complication rate even though the incision started from the orifice of the AV.

Compared with three previous single-armed studies of pre-cut using Iso-Tome<sup>®</sup>,<sup>14-16</sup> the total technical success rate was similar (87.4% in the present study vs 86.4% to 94.3% in the previous studies). However, the primary technical success rate in this study was considerably lower (74.7%). Regarding the complication rate, in the first pilot study of Iso-Tome<sup>®</sup>, the complication rate was 28%.<sup>14</sup> However, two subsequent studies reported complication rates of 2.9% to 6.8%,<sup>15,16</sup> possibly due to the timing of pre-cut after the failure of conventional cannulation. Early pre-cut than delayed rescue use might reduce the rate of adverse events. The overall complication rate in the present study was 9.2%. Regarding NK-F, the technical success and complication rates were comparable to those reported previously.<sup>4,10,11</sup>

Regarding the causes of technical failure of IT-P, a non-prominent AV was the most common cause of primary cannulation failure. IT-P requires hooking onto the orifice of the AV and

**Table 4.** Causes of Precut and Precut Failure as Well as Management

No. (%)	IT-P (n=119)	NK-F (n=120)	p-value
Indication of pre-cut			0.646
Papillary contacts $\geq 5$ times	73 (61.3)	76 (63.3)	
Cannulation time $\geq 5$ min	24 (20.2)	27 (22.5)	
Hook-nose shape	22 (18.5)	17 (14.2)	
Primary causes of pre-cut failure	30 (25.2)	10 (8.3)	0.138
Non-prominent ampulla of Vater	9	3	
Improper targeting*	7	3	
Distortion or bulging d/t tumor invasion	7	4	
Overhanging circular mucosal fold	5	0	
Paradoxical reaction <sup>†</sup>	2	0	
Management of secondary failure	15 (12.6)	6 (5.0)	0.744
PTBD with keeping drainage catheter	1	1	
PTBD with rendezvous	7	2	
PTGBD	2	0	
EUS-guided biliary drainage	0	2	
Surgical intervention	2	1	
Conservative treatment	3	0	

Data are presented as number (%).

IT-P, Iso-Tome<sup>®</sup> pre-cut; NK-F, needle-knife pre-cut fistulotomy; PTBD, percutaneous transhepatic biliary drainage; PTGBD, percutaneous transhepatic gallbladder drainage; EUS, endoscopic ultrasonography.

\*Due to rapid bowel movement, rapid breathing, or anatomical variation during pre-cut; <sup>†</sup>Unexpected endoscopic sedation (midazolam)-related adverse event.

upward incisional traction. Therefore, a non-prominent or flat papilla with a narrow roof or overhanging circular mucosal fold can complicate the creation of an adequate but safe incision. In addition, improper targeting can make it difficult to place/hook the IT-P onto the orifice of the AV. Nevertheless, although this technique was performed by endoscopists experienced with Iso-Tome<sup>®</sup>, the overall failure rate was too high. Stricter indication criteria and training with this device may be warranted. However, the frequency of adverse events did not differ between the two groups. The PEP rate and severity of pancreatitis were also not different between the groups. Despite the high technical failure rate of IT-P, the PEP frequency did not increase, perhaps due to the insulated tip, which did not directly contact the PD.

To perform a successful precut, besides adequate equipment, adequate time for the precut and sufficient experience are required. First, the adequate timing of precut may be related to the DBC criteria. A delayed or rescue trial may increase the rate of adverse events. So, based on previous results, we used the following strict DBC criteria: cannulation time  $\geq 5$  minutes,  $\geq 5$  papillary contacts, or a hook-nose-shaped papilla.<sup>10,11</sup> Among them, the hook-nose-shaped papilla may hamper papillotome access the most, due to the orientation of the AV orifice. Therefore, earlier precut in DBC may reduce procedure time without increasing the frequency of complications, even in inexperienced hands.<sup>10</sup>

Second, regarding experience, European guidelines recommend that precut should be performed only by endoscopists who achieve selective biliary cannulation in  $>80\%$  of cases.<sup>4</sup> However, the quality of evidence was low. Some reports revealed that the success rate of selective biliary cannulation by precut has been reported not to be associated with the experience level of the endoscopist.<sup>10,32,33</sup> In our trial, all endoscopic procedures, including NK and Iso-Tome<sup>®</sup> precut, were performed by two experts because some experience with new instruments, such as Iso-Tome<sup>®</sup> may thus be needed.

Regarding limitations, this study was performed by experienced endoscopists at a single center. NK users may not be accustomed to using the Iso-Tome<sup>®</sup> and there is often a learning curve. In this study we did not estimate about the learning curve of IT-P. Based on our previous reports and experiences, we suggests at least 20 to 30 cases of IT-P might be needed to reach a sufficient level after training of NK-F. Second, not only were two different NK approaches used, but the precut starting position was different for the two methods. For a more precise comparison with IT-P, the conventional precut starting from the papillary orifice should be evaluated. However, because NK-F is safer than a precut starting from the orifice of the AV, IT-P was compared to NK-F. Further research to more fully evaluate the various devices and approaches is warranted. Third, among the DBC criteria, classification of the AV according to its bulging shape may be subject to bias, although there were no significant differences in distribution. In addition, a hooked papilla was

included as a difficult factor that can complicate cannulation, contributing to initial higher cannulation failure rates even for experts. Finally, there should be more stringent indications for the use of IT-P and a training period should be investigated.

In conclusion, our results failed to prove the noninferiority of IT-P compared with NK-F regarding the primary successful selective biliary cannulation rate using the DBC criteria. IT-P also requires a longer successful cannulation time and procedure time. NK-F was more efficient than IT-P in cases of DBC. However, as a primary precut technique, IT-P in cases of DBC was safe and not associated with a higher complication rate even though the incision was started at the orifice of the AV. Users familiar with NK-precut starting from the orifice of the AV may use IT-P alternatively without the increasing risk of PEP.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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