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Transpancreatic biliary sphincterotomy versus double guidewire in difficult biliary cannulation: a randomized controlled trial

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Abstract

Background Difficult biliary cannulation in endoscopic retrograde cholangiopancreatography (ERCP) increases the risk of post-ERCP pancreatitis (PEP). The purpose of this prospective, randomized, multicenter study was to compare two advanced rescue methods, transpancreatic biliary sphincterotomy (TPBS) and a double-guidewire (DGW) technique, in difficult common bile duct (CBD) cannulation.

Methods Patients with native papilla and planned CBD cannulation were recruited at eight Scandinavian hospitals. An experienced endoscopist attempted CBD cannulation with wire-guided cannulation. If the procedure fulfilled the definition of difficult cannulation and a guidewire entered the pancreatic duct, randomization to either TPBS or to DGW was performed. If the randomized method failed, any method available was performed. The primary end point was the frequency of PEP and the secondary end points included successful cannulation with the randomized method.

Results In total, 1190 patients were recruited and 203 (17.1%) were randomized according to the study protocol (TPBS 104 and DGW 99). PEP developed in 14/104 patients (13.5%) in the TPBS group and 16/99 patients (16.2%) in the DGW group ($P = 0.69$). No difference existed in PEP severity between the groups. The rate of successful deep biliary cannulation was significantly higher with TPBS (84.6% [88/104]) than with DGW (69.7% [69/99]; $P = 0.01$).

Conclusions In difficult biliary cannulation, there was no difference in PEP rate between TPBS and DGW techniques. TPBS is a good alternative in cases of difficult cannulation when the guidewire is in the pancreatic duct.

Introduction

In endoscopic retrograde cholangiopancreatography (ERCP), difficult common bile duct (CBD) cannulation is defined according to the European Society of Gastrointestinal Endoscopy (ESGE) criteria as more than 5 minutes attempting to cannulate, more than five contacts with the papilla, or more than one unintended entry into the pancreatic duct (PD) or opacification in wire-guided cannulation (5–5–2 definition) [1]. After persistent attempts with standard methods (e.g. wire-guided cannulation) have failed, access to the CBD often requires the application of advanced cannulation techniques, such as sphincterotome precut, needle-knife precut, and pancreatic guidewire-assisted cannulation with a single wire, proceeding to transpancreatic biliary sphincterotomy (TPBS) or a double-guidewire technique (DGW), pancreatic stenting or papillectomy [1]. However, difficult cannulation and repeated attempts increase the risk of post-ERCP pancreatitis (PEP) to 10.8%–16.2% [1–4].

The aim of the present study was to compare two different advanced cannulation techniques, TPBS and DGW, in terms of PEP and successful cannulation.

Methods

Study design

The recruited patients underwent ERCP between 2015 and 2019 at eight hospitals: Helsinki University Hospital, Oulu University Hospital, Aalborg University Hospital, St. Olavs Hospital in Trondheim University Hospital, Karolinska University Hospital, Oslo University Hospital, Oslo's Rikshospitalet University Hospital, and Turku University Hospital.

The ethical committees of each hospital approved the study protocol. The study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki. The

original study protocol is presented in **Fig. 1s** in the online-only supplementary material.

Patients

The inclusion criteria for recruitment were native papilla, ERCP intended for CBD cannulation, and age over 18 years. The exclusion criteria were acute pancreatitis and no consent for participation in the study. The inclusion criteria for randomization were difficult biliary cannulation and the guidewire entering the PD.

Interventions

ERCPs were performed by experienced endoscopists. PEP prophylaxis prior to ERCP (rectal nonsteroidal anti-inflammatory drugs [NSAIDs] – 100 mg diclofenac or indomethacin for patients without contraindication) was recommended by the study protocol, but implementation was left to the preference of the endoscopist. In addition, prophylactic pancreatic stenting was performed at the discretion of the endoscopist.

Patients fulfilling the inclusion criteria were included. Written informed consent was obtained from all patients prior to ERCP.

Randomization

A randomization list was produced with a random-number generator by using random blocks (size 20) with 1:1 allocation. The allocation of patients was concealed using sequentially numbered, opaque, sealed envelopes. A nurse opened the envelope only after the procedure fulfilled the difficult cannulation criteria and the wire had entered the PD.

ERCP procedure

The TPBS technique was adopted in participating hospitals under the guidance of an expert TPBS endoscopist (J.H.)

The cannulation study protocol (Fig. 1s) was presented at biannual Scandinavian Association for Digestive Endoscopy (SADE) research meetings (March and September 2015 - 2019) in order to inform and encourage more endoscopists and centers to participate in the study, and continuous education assured the quality of TPBS and DGW techniques performed by experienced endoscopists.

Only wire-guided cannulation was used for initial cannulation attempts. The primary cannulation was defined as successful deep biliary cannulation when the guidewire was inside the CBD. If the primary cannulation failed and the 5–5–2 definition of difficult cannulation was fulfilled, the preceding factor leading to difficult cannulation was recorded. All procedures meeting the difficult cannulation criteria and involving the guidewire entering the PD were randomized to either TPBS or DGW.

The randomized method was performed without removing the guidewire from the PD. A time limit of 15 minutes was allowed before the method was regarded as unsuccessful. After 15 minutes, an endoscopist could either change the method or continue the cannulation attempts with the first randomized method.

The success or failure of the randomized method, any additional rescue methods, and the time for successful cannulation or total time used (in cases of final failure) were recorded.

The TPBS technique

The aim of TPBS is to incise the septum between the PD and the CBD in order to expose the bile duct orifice. If a guidewire unintentionally enters the PD, TPBS is performed with a regular sphincterotome and a pure-cut electrosurgical current, toward the 11 or 12 o'clock position. The cut either opens the CBD or reveals the anatomy of the ampulla (**Fig. 1** and **Fig. 2a**, green cut indicates TPBS technique). A further oblique cut toward

the 10 o'clock position, using a needle-knife and starting from the upper end of the previous TPBS, can be performed after the TPBS technique, if required (**Fig. 2**, red cut indicates needle-knife technique). The intention is to cut across to the CBD and expose the lumen [5].

The DGW technique

The DGW technique involves deep PD cannulation using the first guidewire, which may straighten the CBD, thus allowing CBD cannulation with the second guidewire. Therefore, the original guidewire that entered the PD remains in place in order to aid orientation and further attempts to cannulate the CBD are performed using wire-guided cannulation with the second guidewire (**Fig. 3**).

Post procedure

All patients remained in the hospital for at least 4 hours after ERCP and were monitored for the development of PEP, bleeding, cholangitis, perforation, or any other complication.

Serum or plasma amylase was measured 4 hours after the procedure. Thereafter, the patient was discharged at the discretion of the physician. If the patient remained in the hospital overnight, serum or plasma amylase was assayed the following morning.

Definitions and outcomes

The primary outcome was the rate of PEP. Secondary outcomes were successful cannulation with the randomized method within 15 minutes and in total. All other results were considered descriptive.

PEP was defined as the presence of abdominal pain attributable to acute pancreatitis, together with a need for unplanned hospitalization or an extension of a planned hospitalization by at least 2 days, and serum or plasma amylase at least three times

above the upper limit of normal (ULN) at 24 hours after the procedure [6]. PEP was classified as mild, moderate, or severe if the patient had to stay in hospital for less than 4 days, 4–10 days, or more than 10 days, respectively [6].

Success with the randomized method was defined as success when the guidewire entered the CBD. Failure was defined as a failure with the cannulation method used. Final failure was defined as no access to the CBD with any of the methods used.

Any complications, admission times, and any additional care during the first 30 days after the procedure were recorded. In addition, patients were advised to contact the physician at any time if they noticed symptoms such as fever or abdominal pain. We assumed that absence of documented adverse events in the patient records meant that no adverse events occurred.

Sample size calculation

The sample size calculation assumed that 70% of primary cannulations would be successful within the limits of difficult cannulation (i.e. not described as difficult), 30% of all cannulations would be difficult and, of these two-thirds would be randomized (i.e. 20% of total). According to previous studies, the PEP rate was lower following TPBS (0%–10.8% [5,7,8]) than after DGW (17%–38.2% [8–11]). If the 0% rates are ignored, the mean rates were 10% and 25% for TPBS and DGW, respectively. The sample size calculation was performed with power = 0.8 and alpha = 0.05, resulting in 97 patients per randomized group [12].

Statistical analysis

Data were analyzed on an intention-to-treat basis and randomized patients were analyzed according to their original groups. Analyses were performed using IBM SPSS

Statistics for Macintosh, v25.0 (IBM Corp., Armonk, New York, USA) and with R v4.00 software (R Foundation for Statistical Computing, Vienna, Austria).

The primary end point variable was compared using chi-squared and Fisher's exact tests. Statistical significance was assayed as a two-tailed P value of <0.05 . All other statistical tests of outcome results were considered as secondary and their results were taken as descriptive only. In descriptive statistics, continuous variables were described as median (range) or as interquartile range (IQR), and categorical variables were described as number of cases and proportion. Descriptive continuous and ordinal variables were compared using the Mann–Whitney U test and categorical variables were compared using Fisher's exact test.

Results

Patients

A total of 1190 patients underwent ERCP and were recruited between September 2015 and April 2019. The PEP rate among nonrandomized patients who had data available was 4.7% (42/890). The deep biliary cannulation success rate of all ERCPs was 98.8% (1176/1190).

Difficult cannulation

In total, 203 patients (17.1%) met the criteria of difficult cannulation and were randomized (104 to TPBS and 99 to DGW) (**Fig. 4**) The number of recruited patients in each hospital is shown in **Table 1s**. The demographic characteristics of the randomized patients and ERCP procedures are presented in **Table 1**. The median duration of cannulation was 12.5 minutes (IQR 12.7) in the TPBS group and 14.1 minutes (IQR 16.5) in the DGW group ($P = 0.45$).

The cannulation events preceding randomization were (TPBS vs DGW): PD passage/opacification in 82 (78.8%) vs. 68 (68.7%) patients ($P = 0.12$); more than 5 minutes spent attempting to cannulate the CBD in 48 (46.2%) vs. 52 (52.5%) patients ($P = 0.40$); and more than five contacts with the papilla in 35 (33.7%) vs. 30 (30.3%) patients ($P = 0.65$), respectively.

A diverticulum was present in 17/203 (8.4%) patients (7 patients [6.7%] in the TPBS group and 10 patients [10.1%] in the DGW group). In most cases, the papilla was situated at the edge of the diverticulum (11/17 [64.7%]). When a diverticulum was present, cannulation succeeded with the allocated randomized method in 6/7 patients (85.7%) in the TPBS group and in 5/10 patients (50.0%) in the DGW group ($P = 0.30$). All cannulations were finally successful in the TPBS group whereas one failed in the DGW group ($P > 0.99$).

Pancreatic or biliary malignancy was the indication for ERCP in 39/104 patients (37.5%) in the TPBS group and 43/99 patients (43.4%) in the DGW group. In these patients, cannulation succeeded with the allocated randomized method in 32/39 (82.1%) in the TPBS group and in 29/43 (67.4%) in the DGW group. The final cannulation failure rate was not statistically different between the two methods in this patient group (3/39 [7.7%] with TPBS vs. 0/43 [0.0%] with DGW; $P = 0.10$).

In 4/104 patients (3.8%) in the TPBS group and 2/99 patients (2.0%) in the DGW group, trainees were involved in cannulation prior to randomization. In all these cases, trainees were supervised by experts.

Primary outcome – rate of PEP

ERCP complications with TPBS and DGW are presented in **Table 2**. The PEP rate was 14.8% in the whole cohort of patients with difficult cannulation ($n = 203$). There was

no significant difference between the TPBS and DGW techniques in terms of PEP rate (13.5% vs.16.2%, respectively) or the severity of PEP. Among patients with PEP, the median cannulation time was 10.6 minutes (range 6.0–33.9) in the TPBS group and 10.9 minutes (range 3.1–77.7) in the DGW group ($P = 0.61$).

PEP developed in 25/164 patients (15.2%) in the NSAID group and in 5/37 patients (13.5%) in the non-NSAID group ($P > 0.99$).

Cannulation success

Within 15 minutes, deep biliary cannulation was achieved in 81/104 patients (77.9%) in the TPBS group and in 66/99 patients (66.7%) in the DGW group ($P = 0.09$) (**Fig. 4**). If the time limit is disregarded, the success rate of deep biliary cannulation was significantly higher with TPBS (84.6%, $n = 88$) than with DGW (69.7%, $n = 69$; $P = 0.01$). In successfully cannulated TPBS patients ($n = 88$), a needle-knife was also used in 10 procedures (11.4%).

Median time to successful cannulation with the randomized method was 10.6 minutes (IQR 9.6) with TPBS and 9.3 minutes (IQR 9.9) with DGW ($P = 0.52$).

Cannulation with the randomized method failed in 16 patients in the TPBS group and in 30 patients in the DGW group ($P = 0.01$). A needle-knife was also used with TPBS in 4/16 patients. Six TPBS patients and 16 DGW patients underwent a second rescue method after failure of the randomized method before the end of the study protocol time limit of 15 minutes. The additional rescue methods used in TPBS (13 patients) and DGW (30 patients) groups are presented in **Fig. 2s** and **Fig. 3s**, respectively. In the randomized DGW group, TPBS was used as a rescue method after failure in 27/30 patients (90.0%) and successful CBD cannulation was achieved in 21/27 (77.8%). In the randomized TPBS group, DGW was used as a secondary rescue method in 10/16

patients and as a tertiary method in one patient, with final success in 5/11 (45.5%). When comparing the success with these rescue methods (TPBS n = 27, DGW n = 11, none/other n = 8), TPBS seemed to succeed most often ($P = 0.10$). Final failure occurred in seven patients (6.7%) in the TPBS group and two patients (2.0%) in the DGW group ($P = 0.17$).

Discussion

Using the ESGE 5–5–2 definition of difficult cannulation [1], our study showed no difference in PEP rate between the two rescue cannulation methods of TPBS and DGW. However, successful CBD cannulation was significantly greater with the TPBS technique than with the DGW technique.

Primary cannulation success ranged from 70.6% to 88.2% in the participating hospitals. This variation might be due to differences in patient selection and/or the higher volume of more difficult procedures in some of the participating hospitals. In the present study, the rate of difficult cannulation was 203/1190 (17.1%). In previous studies, however, difficult cannulation has varied between 1.4% and 49.5% [13–17]. In the present study, overall cannulation success was high at 95.6% in patients with difficult cannulation and 98.8% among all patients.

PEP is the most common complication of ERCP. Mechanical trauma to the papilla Vateri and the pancreatic sphincter due to repeated cannulation attempts, hydrostatic injury by pancreatic fluids and contrast media, and thermal injury are probable cofactors in the development of PEP [18]. In unselected patients, the incidence of PEP is reported to be 3.5%–4.2% [19,20]. Difficult cannulation and repeated attempts increase this risk of PEP to 10.8%–16.2% [1–4]. In the present study, the PEP rate was 14.8% in difficult

cannulation and 4.7% in all patients. The PEP rate was not significantly different between TPBS and DGW.

There are some commonly accepted patient- and procedure-related risk factors for PEP. Procedure-related factors include difficult cannulation [2,21,22]. Endoscopists' experience as a risk factor is controversial, as some prospective studies have reported it as a significant factor [23,24], while others have not [4,25]. However, in a recent meta-analysis, high-volume endoscopists had 31% lower odds for complications than low-volume endoscopists [26]. In our study, the experience of the endoscopists as a confounding factor was minimal, as only experienced endoscopists performed ERCPs and trainees were involved in only a minority of procedures. The high overall success rate of 98.8% supports this argument.

The TPBS technique was first described by Goff in 1995 [27]. The advantage of TPBS over, for example needle-knife precut alone, is that the depth and location of the incision in relation to the CBD is more controlled [1]. The CBD lumen becomes visible in over half of the procedures [5]. In a prospective study by Kahaleh et al., the success rate with TPBS (n = 116) was 85% and, when combined with the needle-knife technique, this rose to 95% [28]. Furthermore, the overall complication rate in TPBS was 12% and the PEP rate 7.8%, with no difference in PEP rate between conventional biliary sphincterotomy and TPBS.

The DGW method was first described by Dumonceau et al. in 1998 [29]. The technique has been used in cases of complex biliary cannulation, especially in patients with altered CBD anatomy due to neoplasia or atypical morphology of the ampulla [10,29]. A recent meta-analysis compared DGW with other techniques. No significant difference was found in CBD cannulation success; however, TPBS was not included as a comparator technique. DGW significantly increased the risk of PEP [13]. In a Japanese study, the

PEP rate was 22% with DGW alone and 4.7% when combined with prophylactic pancreatic stenting. No pancreatic sphincterotomy was performed [11]. A very low PEP rate (2%) was reported in a prospective study of 50 patients undergoing DGW in Finland, even though none of the procedures included prophylactic pancreatic stenting [30].

The ESGE guideline recommends prophylactic pancreatic stenting when the guidewire inadvertently enters the PD [22]. In our study, only a minority of patients received a prophylactic pancreatic stent (**Table 1**). This was due to the study protocol, which allowed the endoscopist to decide whether or not to place a stent. Even though prophylactic stents were seldom used, the overall PEP rate was comparable between the two techniques. In two recent studies, prophylactic pancreatic stenting did not affect the PEP rate [31,32].

In a South Korean randomized study, TPBS had a lower PEP rate than DGW (10.8% vs. 38.2%) [8]. Sugiyama et al. compared TPBS and DGW, both with prophylactic pancreatic stents, in a randomized controlled trial of 34 patients per group [16]. The cannulation success rate was significantly higher with TPBS (94.1%) than with DGW (58.8%), but the PEP rate was the same in both groups, at 2.9%. In the present study, when the randomized method failed, TPBS was used as a rescue method after DGW in 90.0% of cases, of which 77.8% were successful. In the TPBS group, DGW was used as a rescue method in 62.5% of the patients and success was achieved in half of the cases. Therefore, both are feasible rescue methods when the guidewire is inserted into the PD.

The appearance and size of the papilla, and presence of a periampullary diverticulum or tumor infiltration may influence the outcome of biliary cannulation. In difficult cannulation cases with presence of a periampullary diverticulum, ESGE recommends

selection of cannulation method according to the experience of the endoscopist and the anatomy of the patient [1]. It is difficult or sometimes impossible to proceed with TPBS in patients with intradiverticular papilla or a papilla located in the margin of the diverticulum because of the increased risk of bowel perforation. We suggest that the DGW technique is probably preferable in these situations; however, no definitive data supporting these preferences have been reported.

PD stent placement or use of the DGW technique may secure the papilla in an accessible position. Small or protruding papillae were more difficult to cannulate in a study of 1401 native papillae [33]. ESGE suggests considering the TPBS technique for small papillae in difficult cannulation. However, we prefer DGW for small papillae because of the potential increased risk of perforation with a precutting technique. Prospective comparative studies are warranted to determine the best methods of cannulating papillae with different appearances and in the presence of diverticulum.

Concerns related to long-term complications of TPBS have been expressed [22,34]. A recent retrospective case-control study from Helsinki found similar long-term complication rates between the TPBS group and a control group in which only biliary sphincterotomy was performed [35]. We plan to perform a follow-up study of the present multicenter trial in order to assess the long-term adverse events associated with TPBS. Our present results suggest a preference for TPBS as an advanced method in difficult cannulation; however, the power calculation was not performed to assess the cannulation success rate. Further prospective studies are warranted to seek the preferable cannulation method in difficult biliary cannulation.

Limitations of the study

Although our study is the largest of its kind, consisting of 203 patients, post hoc analysis (see supplementary material) revealed that when comparing the real crossover rates and PEP rates used in sample size calculation, our result is still slightly statistically underpowered (67%–72%) to correctly reject the null hypothesis at the type I error rate.

The ESGE guideline on PEP prophylaxis with rectal NSAIDs was included in our study protocol as a recommendation. Pancreatic stents were used at the discretion of the endoscopists. Only 78.8% of patients in the TPBS group and 82.8% in the DGW group received rectal NSAIDs prior to ERCP. In addition, prophylactic pancreatic stents were seldom used. This might increase the risk of PEP, although there was no difference in prophylaxis between the two study groups. Neither was there a difference in the PEP rate in randomized patients between those who received rectal NSAIDs and those who did not.

It was not possible to randomize all the patients fulfilling the criteria of difficult cannulation. If the guidewire did not enter the PD, patients were not randomized or analyzed as difficult procedures. Median cannulation times between the two study groups were comparable but it should be noted that maximum cannulation times were more than 1 hour in both groups with repetition in the randomized method. Outside clinical trials, these patients would undergo additional cannulation methods sooner to gain access to the CBD. Successful cannulation following crossover between the randomized methods was not considered as a success in the study analysis.

The number of patients recruited and randomized varied between centers, resulting in a potential selection bias in the results.

The protocol time limit of 15 minutes for cannulation attempts using the randomized method was not followed in 16 procedures. It seems that in clinical practice this time limit was too long to follow when the method appeared unsuccessful.

According to the study protocol, ERCP had to be performed by an expert. Only centers that were familiar with both techniques participated in the study. However, in 4/104 TPBS procedures and 2/99 DGW procedures, trainees were involved, and this may prolong the cannulation time unnecessarily. The definition of difficult cannulation was based on a study in which only experts performed ERCP [3]; thus, the time limit of 5 minutes may be too strict in regular clinical practice involving trainees.

A 30-day follow-up was carried out to verify patient records. Minor adverse events may have been missed if a patient did not contact the hospital after discharge.

Conclusion

TPBS and DGW resulted in similar PEP rates. The cannulation success rate with TPBS seemed to be higher than that with DGW. Prospective comparative studies are warranted to determine the best method for cannulation of papillae with different appearances and in the presence of diverticulum. TPBS is a good alternative in cases of difficult cannulation when the guidewire is in the PD; however, it remains a method for experienced endoscopists only.

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Fig. 1 Transpancreatic biliary sphincterotomy technique. CBD, common bile duct; PD, pancreatic duct.

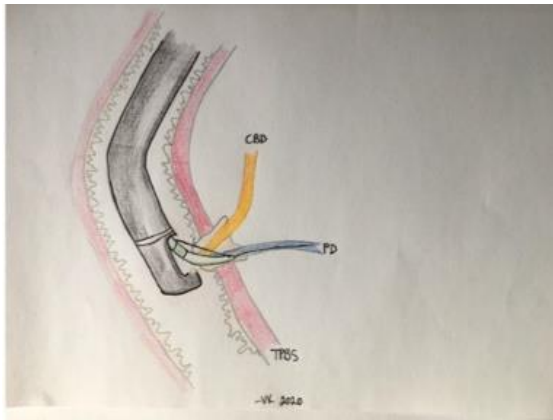
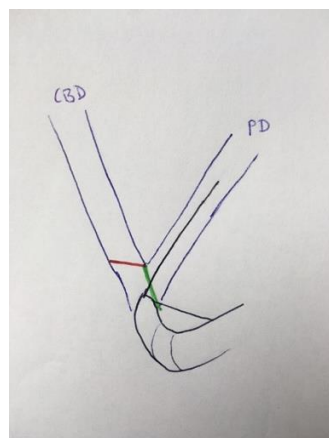


Fig. 2 Transpancreatic biliary sphincterotomy (TPBS) and additional needle-knife technique. **a** Schematic. **b** Endoscopic view. After TPBS, access into the common bile duct (CBD) may succeed either through the papilla, through the upper corner of the cut, or after oblique needle-knife cut across the CBD. PD, pancreatic duct; green line, line of sphincterotomy; red line, additional needle-knife cut.

a



b

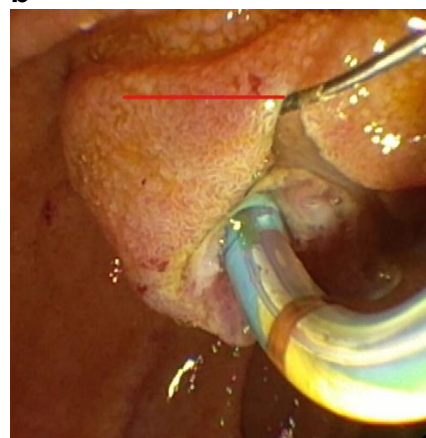


Fig. 3 Double-guidewire technique. **a** Schematic. **b** Endoscopic view. CBD, common bile duct; PD, pancreatic duct.

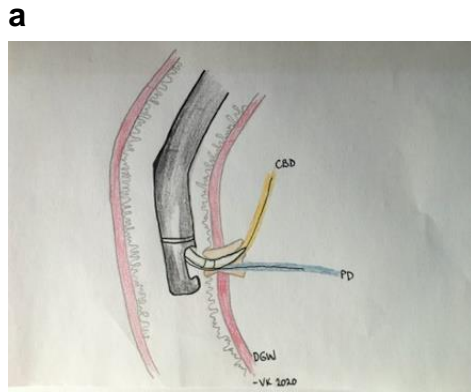


Fig. 4 CONSORT flow diagram of recruited and randomized patients. Data are presented as the number of patients. ERCP, endoscopic retrograde cholangiopancreatography; WGC, wire-guided cannulation; PD, pancreatic duct; TPBS, transpancreatic biliary sphincterotomy; DGW, double-guidewire technique; pt, patients.

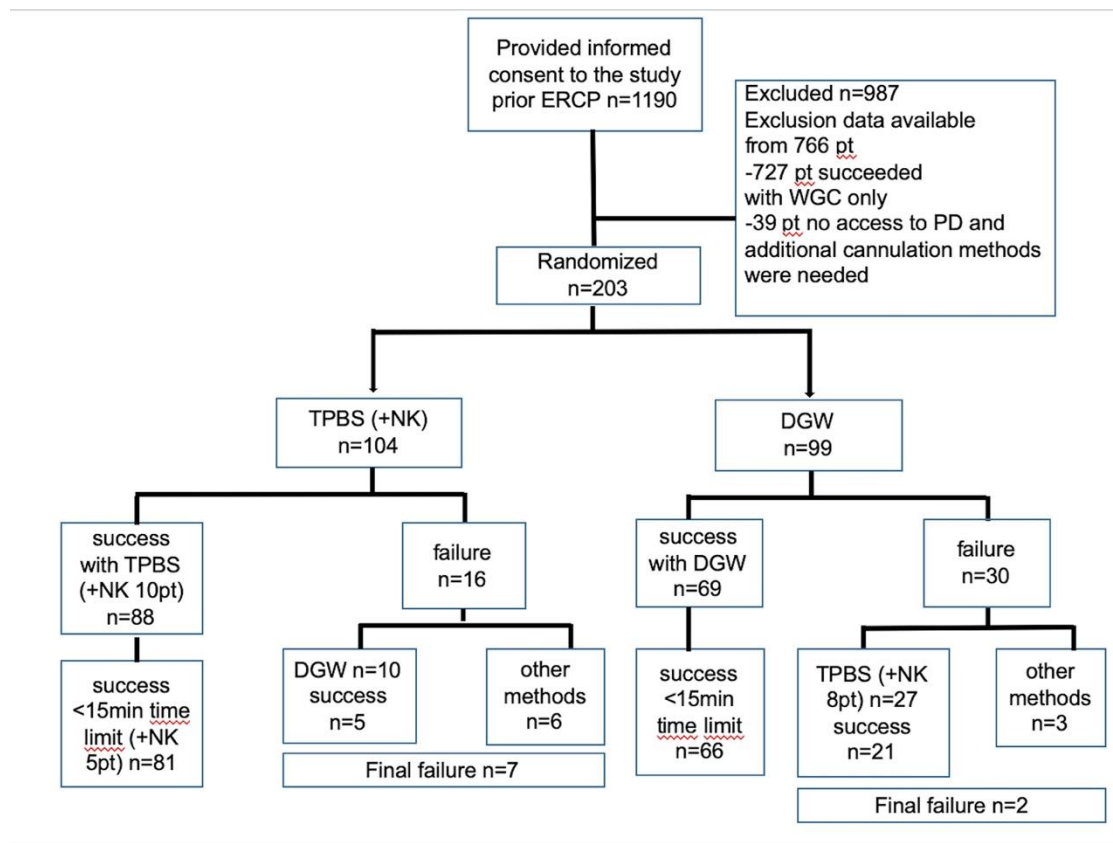


Table 1 Demographic data of the randomized patients and endoscopic retrograde cholangiopancreatography procedures.

	TPBS n = 104	DGW n = 99	<i>P</i> value
Age, median (range), years	66 (21–97)	68 (24–92)	0.47
Female sex, n (%)	46 (44.2)	59 (59.6)	0.04
NSAID as a PEP prophylaxis, n (%)	82 (78.8)	82 (82.8)	0.72
Indication for ERCP, n (%)			
CBD stones	47 (45.2)	40 (40.4)	0.48
Stricture	43 (41.3)	48 (48.5)	0.33
PSC	6 (5.8)	6 (6.1)	>0.99
Post cholecystectomy (bile leakage)	8 (7.7)	9 (9.1)	0.80
Post LTX (stricture)	0 (0)	1 (1.0)	0.49
Post other surgery	0 (0)	2 (2.0)	0.24
Other	8 (7.7)	9 (9.1)	0.80
Prophylactic pancreatic stent	9 (8.7)	11 (11.1)	0.64

TPBS, transpancreatic biliary sphincterotomy; DGW, double-guidewire technique; NSAID, nonsteroidal anti-inflammatory drug; PEP, post-ERCP pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; PSC, primary sclerosing cholangitis; LTX, liver transplantation.

Table 2 Complications of endoscopic retrograde cholangiopancreatography.

	TPBS n = 104	DGW n = 99	P value
PEP, n (%)	14 (13.5)	16 (16.2)	0.69
PEP severity, n (%)			0.19
Mild	7 (6.7)	9 (9.1)	>0.99
Moderate	4 (3.8)	7 (7.1)	0.47
Severe	3 (2.9)	0 (0.0)	0.09
Other complications total, n (%)*	3 (2.9)	5 (5.1)	0.49
Bleeding, n (%)	0 (0.0)	1 (1.0)	0.49
Perforation, n (%)	2 (1.9)	1 (1.0)	>0.99
Cholangitis, n (%)	1 (1.0)	2 (2.0)	0.61
Other infection, n (%)	0	2 (2.0)	0.24

TPBS, transpancreatic biliary sphincterotomy; DGW, double-guidewire technique; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis. * Patients could have more than one complication.

SUPPLEMENTARY MATERIAL

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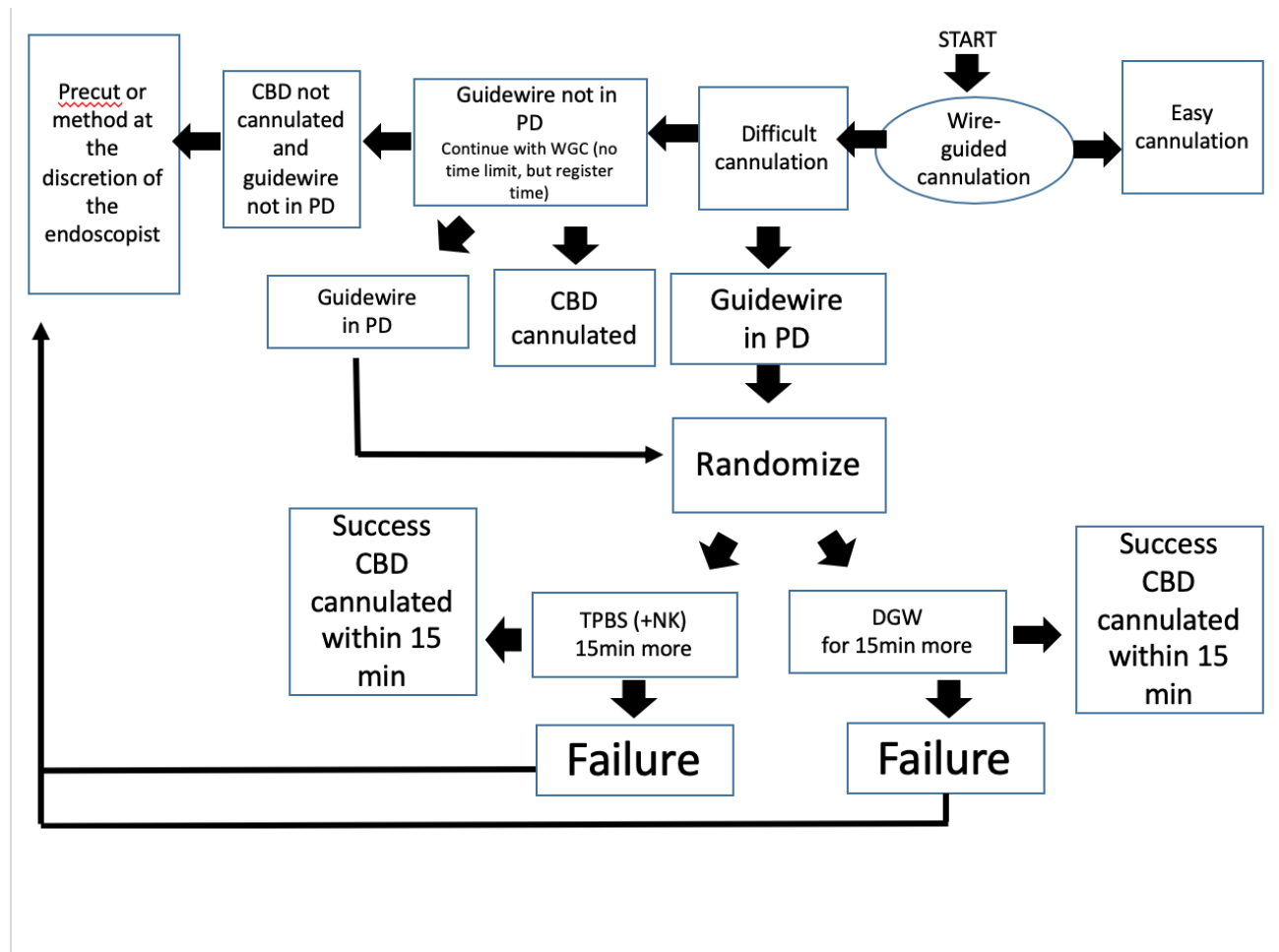
**TRANSPANCREATIC BILIARY SPHINCTEROTOMY OR DOUBLE
GUIDEWIRE IN DIFFICULT BILIARY CANNULATION: A RANDOMIZED
PROSPECTIVE STUDY BY SCANDINAVIAN ASSOCIATION FOR
DIGESTIVE ENDOSCOPY**

Table 1s. Patients from the participating hospitals

	AAL- BORG	HEL- SINKI	HUD- DINGE	OSLO RIKS- HOSPI- TALET	OULU	TROND- HEIM	TURKU	OSLO ULLEVÅL	TOTAL
TPBS	11	45	16	1	10	8	12	1	104
DGW	8	39	17	1	9	8	13	4	99
not randomized	47	325	211	9	153	44	186	12	986
percentage randomized	28.8%	20.5%	13.5%	18.2%	11.0%	26.6%	11.8%	29.4%	17.1%
TOTAL	66	409	244	11	172	60	211	17	1190

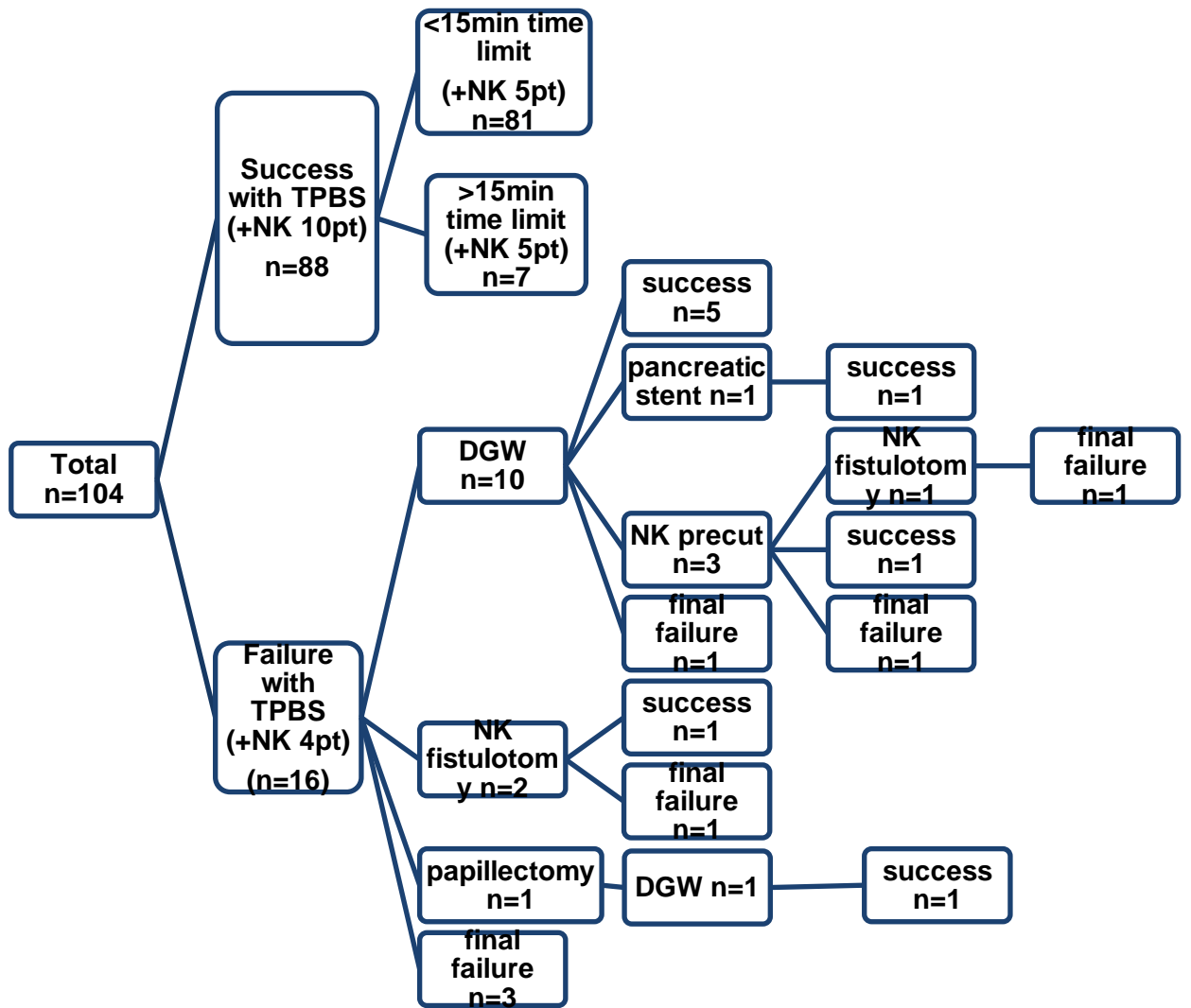
Data is presented as the number of patients
 TPBS transpancreatic biliary sphincterotomy
 DGW double guidewire technique

Figure 1s. Original study protocol.



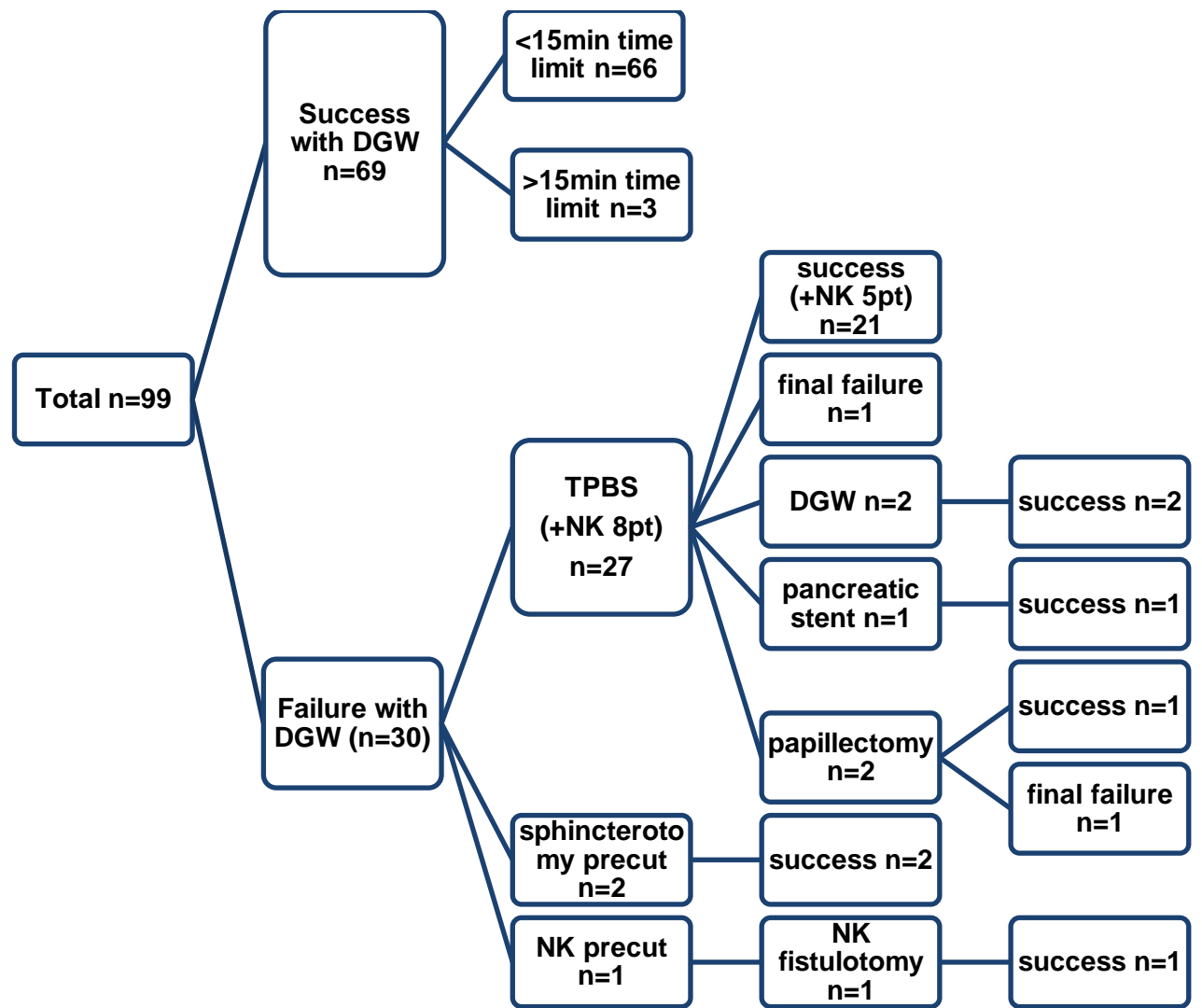
TPBS transpancreatic biliary sphincterotomy
 NK needle knife
 DGW double guidewire technique
 CBD common bile duct
 PD pancreatic duct
 WGC wire guided cannulation
 min minutes

Figure 2s. Flowchart TPBS group and procedures after failure in the first randomized method



Data is presented as the number of patients
 DGW double guidewire technique
 NK needle knife
 pt patients
 min minutes

Figure 3s. Flowchart DGW group and procedures after failure in the first randomized method



Data is presented as the number of patients
 TPBS transpancreatic biliary sphincterotomy
 NK needle knife
 DGW double guidewire technique
 min minutes
 pt patients

Power calculation

We performed post hoc statistical power calculations using R 4.00 software and pwr-package. Using PEP rates of 10% in TPBS and 25% in DGW (as in sample size calculation) and real crossover rates of 9.6% and 27.3%, respectively, we ended up to have 72.4% probability of rejecting the null hypothesis at type I error rate of 0.05 power.

In addition, we performed calculations using the PEP rates of 7.4% from Pècsi et al Dig Dis Sci 2019 (ref 34) in TPBS (only RCTs) and 20.1% in DGW from Tse et al Endoscopy 2017 (ref 13) (RCTs with full text and similar setting), and same crossover rates as before. Then, the power decreased to 66.9%.