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A muticenter prospective randomized study of selective bile duct cannulation performed by multiple endoscopists: The BIDMEN study

Short title: Biliary cannulation RCT for types of methods and catheters

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Background: Wire-guided cannulation (WGC) with a sphincterotome for selective bile duct cannulation (SBDC) has been reported to have a higher success rate and lower incidence of post-ERCP pancreatitis (PEP) than conventional methods in some randomized controlled trials (RCTs) that were both single-center and limited to only a few endoscopists.

Objective: To estimate the difference in SBDC according to the method and catheter used in a multicenter and multi-endoscopist study.

Design: A prospective multicenter RCT with a 2-by-2 factorial design.

Setting: Fifteen referral endoscopy units.

Patients: In total, 400 consecutive patients with naïve papilla who were candidates for ERCP were enrolled and randomized.

Interventions: Patients were assigned to 4 groups according to combined catheter (sphincterotome (S) or catheter (C)) and method (with/without guidewire (GW)).

Main Outcome Measurements: Success rate of SBDC in 10 min, time for SBDC, fluoroscopic time and incidence of complications.

Results: There was no significant difference in SBDC success rate between with- and without-GW, between C and S, or between the 4 groups (C+GW, C, S+GW, and S). WGC had a tendency to significantly shorten cannulation and fluoroscopic times only in approximately 70% of patients in this study in whom SBDC was achieved in 10 min or less (P = 0.036 and 0.00004, respectively). All 4 groups resulted in similar outcomes in PEP (4%, 5.9%, 2%, and 2.1%, respectively).

Limitations: Non-double-blinded study.

Conclusions: WGC appears to significantly shorten cannulation and fluoroscopic times. However, neither the method nor type of catheter used resulted in significant differences in either SBDC success rate or incidence of PEP in this RCT.

Keywords:

Wire-guided cannulation; Selective bile duct cannulation; Post-ERCP pancreatitis; Randomized controlled trial; Cannulation time; Fluoroscopic time; Radiation exposure time

INTRODUCTION

Biliary cannulation is the most basic procedure for performing biliary interventions; however, no standard has been established to date. The success rates are considered to be related to 3 factors: the kind of catheter, cannulation method, and the skill of the endoscopist. The complication rates are also related to 3 factors: patient, procedure factors, and operator expertise. Cannulations using a sphincterotome with wire-guided cannulation (WGC) instead of the conventional catheter, with contrast medium injection, are gradually performed in many countries. These new methods were reported to be superior to conventional techniques in terms of both success rate and the incidence of post-ERCP pancreatitis (PEP) in some randomized studies [1-5]. However, those studies were performed by either a single or, at most, two skilled endoscopists in a single center [1,2,4,5]. Thus, these data cannot be generalized more widely.

In these previous studies, 5° backward-oblique angle therapeutic duodenoscopes (BOAD) were used. In Japan, standard duodenoscopes have traditionally been 15° BOAD. Thus, cannulation methods used in Japan and other countries differ. We previously reported that using a 15° BOAD yielded a superior biliary cannulation success rate, compared with a 5° BOAD, and did not require the bow-up function of the sphincterotome [6].

As mentioned above, we conducted a prospective multicenter randomized controlled trial using a two-by-two factorial design, and assessed conventional ERCP catheter versus sphincterotome and WGC versus catheter cannulation with contrast medium injection based on multiple endoscopists using a 15° BOAD in order to estimate the difference in SBDC according to the method and catheter used in a multicenter and multi-endoscopist study. Here, we designated this RCT as the BIDMEN study (a

multicenter prospective randomized study of selective "***bi***"le "***d***"uct cannulation performed by "***m***"ultiple "***en***"doscopists).

PATIENTS AND METHODS

Study design

This study was conducted as a prospective, randomized controlled multicenter trial by multiple endoscopists using a two-by-two factorial design: conventional catheter versus sphincterotome and WGC versus catheter cannulation with contrast medium injection. Enrolled patients were assigned to 4 groups according to both catheter type (sphincterotome (S) or catheter (C)) and method (with/without guidewire (GW)): C+GW, C, S+GW, and S. We also compared with- and without-GW groups, and S and C groups.

The goal was to enroll 100 patients in each of the 4 groups, yielding combined data for 200 patients in each group for the 2 main cannulation method comparisons (catheter and sphincterotome groups).

The study protocol was approved by the ethics committees of each participating institute and was performed at each hospital according to the guidelines of the Declaration of Helsinki for biomedical research involving human subjects. All participants gave prior written informed consent.

Eligibility criteria

The study group included patients who required cholangiography and had an intact papilla of Vater. Exclusion criteria were as follows: age less than 20 years, a value of more than 3 in performance status according to the scale of the Eastern Cooperative Oncology

Group [7], mental disability, contrast medium allergy, severe heart disease, severe pulmonary disease, history of previous endoscopic sphincterotomy, previous endoscopic balloon dilatation, ampullary neoplasm, infiltration of the papillary area by pancreatic cancer, acute pancreatitis, chronic pancreatitis with an acute exacerbation at the time of the ERCP, impacted common bile duct (BD) stone, Billroth II gastrectomy, Roux-en-Y reconstruction, separate papillary orifices of the common BD and pancreatic duct, anomalous pancreaticobiliary channel, long-common channel, pregnancy, possibly pregnancy, women wishing to become pregnant, nursing mothers, and refusal to provide informed consent.

Randomization

Randomization of patients was performed according to a computer-generated schedule. Randomization was performed just before the ERCP procedure, with stratification by each endoscopic unit. The patients were enrolled via a dedicated website and the method of selective BD cannulation (SBDC) identified just after enrollment. The person generating the randomization schedule was not involved in determining patient eligibility, administering treatment, or determining outcome.

Study protocol

ERCP was performed using a 15° BOAD with an elevator function (JF-240, JF-260V or TJF-260V; Olympus Medical Systems Corp., Tokyo, Japan). An ERCP catheter was used corresponding to the 0.035-inch GW (PR-104Q-1, PR-106Q-1, and PR-V234Q; Olympus, Fluoro Tip^{TM}, Tandem^{TM} XL; Boston Scientific Japan, Tokyo, Japan and article No. 0131110 or 0130211; MTW Endoskopie, Wesel, Germany). A CleverCut3V ^{TM} with a tip

length of 7 mm and a cutting wire length of 20 mm was used as a sphincterotome (KD-V411M-0720, Olympus). Contrast medium was used as a standard monomer-ionic, iodinated, radiological contrast agent with 60% iodine. As a GW, a standard 0.035-inch hydrophilic hard type GW (Jagwire^{TM}, straight type, Boston) was used. All endoscopic procedures were performed while the patient was under conscious sedation. This study was performed at tertiary referral endoscopic units, which had a dedicated ERCP training fellow. For each endoscopic unit, at least one senior endoscopist with a total career length of more than 10 years, experience with 2,000 ERCPs, or an annual ERCP caseload of over 200, performing or directly supervising all procedures. On the basis of the total career length, operator expertise was defined as low if 4 years or less, moderate if 5–9 years, and high if 10 years or more.

Selective bile duct cannulation technique

With regard to contrast medium, cannulation using an ERCP catheter/sphincterotome was performed as follows. An ERCP catheter/sphincterotome without a GW was inserted into the working channel of the duodenoscope. After viewing the duodenal papilla from the front, time measurement was started when BD cannulation was attempted. From inside the orifice of the duodenal papilla, the contrast medium was gently and carefully injected into the BD under X-ray fluoroscopic guidance. SBDC was checked by performing cholangiography. If direct BD cannulation was not achieved, test injections of contrast medium were used to visualize the BD and the ERCP catheter/sphincterotome was reinserted deeply with the help of cholangiography. Successful cholangiography without SBDC was defined as failure of SBDC. Regarding contrast medium cannulation techniques, use of a GW was banned until the BD was cannulated.

Regarding GW cannulation using an ERCP catheter/sphincterotome, it was performed as follows. An ERCP catheter/sphincterotome preloaded with a GW was inserted into the working channel of the duodenoscope. After viewing the duodenal papilla from the front, time measurement was started when BD cannulation was attempted. From either outside the orifice of the duodenal papilla or inside the orifice, the GW was gently and carefully advanced under the guidance of X-ray fluoroscopy and inserted into the BD. If a GW could not be inserted into the BD, it was retracted and another attempt was made. After inserting the GW into the BD, the ERCP catheter/sphincterotome was inserted deep into the BD along the GW. SBDC was checked by visually confirming bile or performing cholangiography. GWs were controlled by an assistant endoscopist, and use of a contrast agent was not allowed until the BD was cannulated.

Selective bile duct cannulation protocol

In each group, BD cannulation was started with a time limit of 10 min. In principle, the SBDC was set a time limit within 5 min for the low or moderate career-length of ERCP experience in this study. If the SBDC was not possible within 10 min, then there were no subsequent restrictions on centers or endoscopists. Precutting techniques also included freehand needle-knife papillotomies and traction-type pancreatic precuts using a sphincterotome. Additionally, no restriction was placed on the use of contrast medium. At the end of the procedure, all techniques used for SBDC were recorded.

Outcome measures

The primary study endpoint was success rate of SBDC within 10 min. The secondary endpoints were as follows: 1) time for SBDC, 2) fluoroscopy time for SBDC, 3) number of attempts at BD cannulation, 4) number of pancreatic opacifications, 5) number of accidental pancreatic duct insertions, 6) use of precutting for SBDC, 7) final success rate of SBDC, and 8) complications. Based on the Cotton classification [8], the diagnostic criteria for PEP were abdominal pain lasting more than 24 h after ERCP and hyperamylasemia greater than three times the upper limit of the normal range. The definition of severity was modified based on the Cotton criteria [8]. However, although the Cotton criteria defined the degree of severity as days of hospitalization, each institution used the same number of days of fasting. Serum amylase was measured 24 h after ERCP. The other complications followed the original classification. Hyperamylasemia was defined as an increase in serum amylase to more than 3 times the upper limit of the normal limit defined by each institution.

Intention-to-treat (ITT) and per protocol (PP) methods were used in the analysis. ITT analysis was based on the original total cohort of patients enrolled. PP analysis was based on the subset of patients in whom SBDC was attempted. Rates of successful SBDC and complications were evaluated by ITT analysis. The time for SBDC, fluoroscopy time for SBDC, number of attempts for SBDC, and accidental pancreatic duct opacification/insertion were all evaluated by PP analysis.

If a low or moderate career-length of ERCP experience could not achieve SBDC, and then high career-length of ERCP experience could achieve SBDC within 10 min, these were defined as success of SBDC based on ITT analysis.

Sample size

Katsinelos et al. reported that success rates for SBDC using a conventional ERCP catheter were 50-67% [4], while Bailey et al. [3], Abraham et al. [9], and Maydeo and Borkar [10] reported rates of 73.9-85% for SBDC using a sphincterotome combined with contrast medium, and Bailey et al. [3] and Lee et al. [5] reported rates of 81.4-95% for SBDC using a sphincterotome combined with a GW. Given these results, the sample size calculation for the present study was based on an assumption of an 85% success rate for SBDC with an ERCP catheter combined with contrast medium and a 95% success rate with a sphincterotome combined with a GW. More than 86 patients in each study group were thus required for a 5% significance level and a statistical power of 80% in a two-sided equivalence test. A total of 400 patients were enrolled, because about 10% of subjects were expected to be lost due to the inclusion and exclusion criteria and follow-up.

Statistical analysis

The number of procedures started, success of SBDC within 10 min, fluoroscopy time, number of attempts, final SBDC success rate, and SBDC complications in the four groups were compared according to operator expertise. Multiple logistic regression models were also used to compare the “Catheter group or sphincterotome group” and the “With-GW group or without-GW group” as explanatory variables. We compared pancreatic opacification between the C and S groups, and accidental pancreatic duct insertion between the C+GW and S+GW groups.

Fisher’s exact probability or chi-squared tests were used for binary outcomes, and Wilcoxon’s rank sum test for numerical outcomes. The significance level was defined at

0.05. In comparisons between the 2 combined groups, the significance level was defined as 0.0083 (0.05 divided by 6) according to Bonferroni's method. Factors with $P < 0.10$ by logistic regression analysis were considered to be potential risk factors for SBDC and were further analyzed in a multiple logistic regression model. Statistical analyses were performed using HALBAU for Windows (ver. 7.1; CMIC, Tokyo, Japan).

This trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, number UMIN000002572.

RESULTS

Patients

This study was performed between September 2009 and March 2010 in 15 referral endoscopic units. The baseline data of the 4 groups were well balanced (Figure 1, Table 1).

Selective bile duct cannulation within 10 minutes

There was no significant difference in SBDC success rates within 10 min between the catheter and sphincterotome groups, or the with-GW and without-GW groups (Table 2). The 4 groups showed no significant difference in SBDC success rate: C group, 71.3% (72/101); C+GW group, 73.5% (75/102); S group, 68% (68/100); and S+GW group, 69.1% (67/97).

Procedure times

The median time to SBDC within 10 min in the with-GW group (median, 121 s) was significantly shorter than that in the without-GW group (median, 178 s; $P = 0.036$; Table 2). This analysis was performed only using cases of successful cannulation within 10 min. On the other hand, there was no significant difference between either the catheter and sphincterotome groups, or among the 4 subgroups (Table 3-1).

The median time to SBDC in the with-GW group (median, 170 s; 25 percentile, 79 s; 75 percentile, 612 s) was a tendency to significantly shorter than that in the without-GW group (median, 305 s; 25 percentile, 107 s, 75 percentile, 690 s, $P = 0.05761$) with all patients (including time for SBDC longer than 10 min).

We also analyzed the SBDC fluoroscopy time. The time to SBDC within 10 min in the with-GW group (median, 15 s) was significantly shorter than that in the without-GW group (median, 36 s; $P = 0.00004$; Table 2). Of the 4 subgroups, the S group (median, 62.7 s) had a significantly longer fluoroscopy time than either the C+GW (median, 38.7 s) or S+GW group (median, 34.1 s; $P < 0.05$; Table 3-1).

Numbers of attempts for selective bile duct cannulation

This analysis was performed only using cases of successful cannulation within 10 min. There was no significant difference in the numbers of attempts for SBDC between the 4 subgroups: C group (average, 3.3 times), C+GW group (3.3 times), S group (3.4 times), and S+GW (3.3 times).

Pancreatic opacification, accidental pancreatic duct insertion

There was no significant difference in pancreatic opacification between the C (52%; 52/100) and S (58.8%; 57/97) groups. We also analyzed accidental pancreatic duct insertion. However, there was no significant difference between the C+GW (47.5%; 48/101) and S+GW (51.5%; 50/92) groups (Table 3-1). The rates of cases with placed pancreatic stent or naso-pancreatic drainage were 12.9% (13/101), 3.9% (4/102), 7% (7/100), and 8.2% (8/97). The 4 subgroups showed no significant differences in pancreatic stent/naso-pancreatic drainage rates (Table 4).

Use of precut for selective bile duct cannulation

There was no significant difference in the rate of precut between the C and S groups, or the with-GW and without-GW groups. The 4 subgroups showed no significant difference in the rate of precut: C group, 4% (4/101); C+GW group, 5.9% (6/102); S group, 4% (2/100); and S+GW group, 2.1% (2/97; Table 3-1).

Final success rate of selective bile duct cannulation

There was no significant difference in final SBDC success rate between the C and S groups or the with-GW and without-GW groups. The 4 subgroups showed no significant difference in SBDC success rate: C group, 94.1% (95/101); C+GW group, 94.1% (96/102); S group, 95% (95/100); and S+GW group, 92.8% (90/97; Table 3-1). Results of various methods of final SBDC over 10 min in each subgroup are shown in Table 3-2.

Complications

There was no significant difference in PEP between the ERCP catheter and sphincterotome groups or the with-GW and without-GW groups. The 4 subgroups showed no significant difference in PEP rate: C group, 4% (4/101) [mild/moderate/severe: 2/1/1]; C+GW group, 5.9% (6/102) [mild/severe: 3/3]; S group, 2% (2/100) [mild/moderate: 1/1]; and S+GW group, 2.1% (2/97) [mild/severe: 1/1]. No significant difference was found in the rates of hyperamylasemia between the 4 subgroups: C group, (14.9%; 15/101); C+GW group, (19.6%; 20/102); S group, (13%; 13/100); and S+GW (19.6%; 19/97). As a GW-related complication, two cases with ampulla of Vater perforation were noted in each GW group; these were minor and resolved without therapy (Table 4). These ampulla of Vater perforations were caused by the GW passed through the posterior wall of the ampulla of Vater.

Comparison of selective bile duct cannulation and complications with regard to operator expertise

The fluoroscopy time for SBDC and numbers of attempts at SBDC were measured only using cases of successful cannulation within 10 min. With regard to operator expertise, the rates of cases started by operators with low ERCP experience were 36.6% (37/101), 39.2% (40/102), 31% (31/100), and 38.1% (37/97) in the C, C+GW, S, and S+GW groups, respectively. The rates of cases started by operators with moderate ERCP experience were 34.7% (35/101), 25.5% (26/102), 28% (28/100), and 28.9% (28/97) in the C, C+GW, S, and S+GW groups, respectively. The four subgroups showed no significant difference in the rates of cases started by operators with low/moderate/high ERCP experience.

No significant difference was found in the rate of SBDC success within 10 min, final success rate of SBDC, fluoroscopy time for SBDC, number of SBDC attempts, or complications among the three levels of ERCP experience. However, the time required for SBDC in the high ERCP experience group was significantly shorter than those in the low and moderate ERCP experience groups ($P = 0.003$).

The following 8 factors for SBDC were extracted and subjected to univariate analysis: age, gender, method of biliary cannulation, underlying disease (benign biliary/pancreatic disease, malignant biliary/pancreatic disease), intradiverticular papilla, with/without gallbladder, with/without gallbladder stone and operator expertise (low, moderate, and high ERCP experience). Malignant biliary disease, with gallbladder, without gallbladder stone and moderate ERCP experience were potential risk factors for failure of SBDC within 10 min, with $P < 0.10$ in univariate analyses. However, no statistically significant factor was found using a multiple logistic regression model (Table 5).

DISCUSSION

In this study, we considered 3 factors: catheter type, cannulation method, and endoscopist skill. To the best of our knowledge, this is the first report of a trial involving multiple centers and endoscopists. Neither catheter type nor cannulation method had any significant effect on SBDC success rate. However, the SBDC and fluoroscopy times were significantly shorter in the with-GW group.

The success rates of SBDC within 10 min among the 4 groups in this study constitute seemingly ordinary data compared with some RCTs [3-5]. However, the final success rate of SBDC was acceptable (92.8–95%). The rate of precutting was 2.1-4% in

this RCT. The rates of precutting in previous representive RCTs were 0% [1], 8.7-22% [2], 12.4-13.7% [3], 15-18.3% [4], 18.7-24% [5], and 3.5-4.7% [6]. The rate of use of precutting in the study of Lella et al. [1] can be exceptional; however, our rates of use of precutting were as well as or lower than those of previous RCTs (Table 6). The rate of PEP was 2-5.9% in this RCT. The rates of PEP in previous RCTs were 0-4% [1], 8.7-16.7% [2], 6.2-7.9% [3], 5.4-7.9% [4], 2-11.3% [5], and 2.3-5.8% [6]. Our rate of PEP was good compared with those of previous RCTs (Table 6).

Because this RCT was performed by multiple endoscopists, mixed operator expertise may have lowered the success rate of SBDC within 10 min compared with previous RCTs [1-5]. However, these results may be standardized, based on a multicenter RCT. This study was designed to allow 10 min for the initial SBDC. The reported time limits within which the regularly used SBDC technique is used vary between 10 and 30 min [3-6,11-13]. The 15- to 30-min limits are used less consistently [14-20]. More refined methodology appears to be necessary to clarify the definition of the allocated procedure time regarding SBDC.

These results suggested that BD cannulation ability was not improved by the introduction of sphincterotomes and WGC with the participation of multi-endoscopists and using a 15° BOAD. These results may not be applicable to situations in which a 5° BOAD is used to perform ERCP. Recently, a single-center RCT using 15° BOAD with multiple operators comparing the practice of SBDC using a conventional catheter with WGC was reported from Japan [21]. The study revealed that a WGC did not improve the success rate of SBDC, and did not reduce the PEP (Table 6). We think that the bow-up sphincterotome function may be useful when using a 5° BOAD, because of its poor ability to adjust the BD axis merely by scope maneuver [6]. The most important step of

selective cannulation was adjustment of the catheter to the BD axis, and a 15° BOAD could readily perform this step without a bow-up function, but a 5° BOAD could not do so. We should thus consider the BOAD maneuver during SBDC with emphasis on the ability to adjust to the BD axis.

In successful cannulation cases, the procedure time to cannulation in the with-GW group was significantly shorter than that in the without-GW group. Sometimes, SBDC using a catheter was difficult and successful injection of contrast medium into BD required a lengthy period. The data in this study suggest that WGC may improve this step, because of the omission of contrast medium injection, and appeared to shorten the procedure and radiation exposure time, which will result in protecting both patients and endoscopists from unnecessary radiation exposure.

Previous studies reported that WGC decreased the incidence of pancreatitis; however, in this study, no such decrease was detected. Previous studies may have been performed by endoscopists highly skilled in WGC. PEP remains a serious problem for endoscopists and must be resolved.

With regard to PEP, no significant differences were found among each group. However, the data differed among each group. Therefore, if the number of enrolled patients is increased than this study, then there will be potentially significant differences in PEP.

Some minor complications were observed in the with-GW group, including the ampulla of Vater perforation, which may have occurred through the use of GW. Thus, careful maneuvering of the GW is essential. Recently, we reported a portobiliary fistula complicated with WGC during ERCP [11]. More attention should be paid to the possibility of WGC-related portobiliary fistulas while using the WGC.

As a GW, this RCT used a standard 0.035-inch hydrophilic GW (straight type). Regarding the kind of GW, there were various sizes and tips. However, to date, no reported RCT has compared a standard size GW (0.035-inch) with a smaller GW (0.025-, 0.021-, or 0.018-inch) or standard GW (straight type) with an angle-tipped GW. The use of a smaller GW may minimize the risk of papillary or pancreatic trauma and PEP. Larger studies are required to further examine the effects of the size and tip of the GW in WGC.

One limitation of this study is the non-double-blinded clinical setting. Furthermore, the procedures performed by multiple endoscopists in multiple centers may have caused bias due to differences in skill.

In conclusion, WGC did not improve the success rate for biliary cannulation and PEP compared with the conventional contrast technique using a 15° BOAD in a multicenter study. However, WGC appears to decrease cannulation/fluoroscopy time for SBDC compared with non-GW cannulation.

TAKE-HOME MESSAGE

- ✓ This randomized, controlled trial showed no significant difference between with- and without- guidewire, or between catheter and sphincterotome with regard to selective bile duct cannulation (SBDC), numbers of attempts, use of precut, or post-ERCP pancreatitis in multicenter and multiple endoscopist settings.
- ✓ However, wire-guided cannulation appeared to significantly shorten cannulation and fluoroscopic times for SBDC compared with non-guidewire cannulation.

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Conflict of interest statement

We declare that we have no conflict of interest.

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Appendix

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Table 1. Baseline patient characteristics

	C group	**C+GW group**	**S group**	**S+GW group**
No. of patients	101	102	100	97
Median age (range)	68.2 (29-94)	67.4 (25-96)	66.7 (33-90)	68.5 (27-92)
Gender				
Male/Female	56/45	70/32	65/35	62/35
Diagnostic/therapeutic ERCP	12/89	11/91	15/85	11/86
Intradiverticular papilla	32	18	24	26
Gallbladder				
With/without	80/21	72/30	76/24	77/20
Gallbladder stone	44	33	39	37
Indications for ERCP				
Benign biliary disease	63	55	56	55
Choledocholithiasis	58	40	46	40
Cholangitis	-	6	3	7
Benign biliary stricture	3	4	5	5
SOD	-	-	-	-
Others	2	5	2	3
Malignant biliary disease	22	31	25	29
Cholangiocarcinoma	12	20	15	14
Gallbladder carcinoma	6	6	6	3
Cholangiocellular carcinoma	2	-	1	3
Others	2	5	3	9
Benign pancreatic disease	6	4	2	1
Chronic pancreatitis	-	-	-	1

Autoimmune pancreatitis	1	1	1	-
Previous acute pancreatitis	1	-	-	-
Others	4	3	1	-
Pancreatic carcinoma	10	12	17	12

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction

Table 2. Results of selective bile duct cannulation between the guidewire (GW) (ERCP catheter/sphincterotome with GW) and without GW (ERCP catheter/sphincterotome without GW) groups

	With GW group	**Without GW group**	
No. of patients	201	199	
SBDC within 10 min	142 (70.6%)	140 (70.4%)	N.S.
Time for SBDC within 10 min *			
Median seconds (25 percentile, 75 percentile)	121.5 (53, 251)	178 (60, 364)	$P = 0.036$
Fluoroscopic time for SBDC within 10 min *			
Median seconds (25 percentile, 75 percentile)	15 (6, 45)	36 (12, 79)	$P = 0.00004$

SBDC, selective bile duct cannulation; N.S., not significant

Excluded cases were 9 cases from the GW group (4 cases from the ERCP catheter with GW /without contrast medium group and 5 cases from the sphincterotome with GW /without contrast medium group) and 4 cases from the without GW group (1 case from the ERCP catheter with contrast medium/without GW group and 3 cases from the sphincterotome with contrast medium/without GW group).

* Calculated in successful cases alone.

Table 3-1. Results of selective bile duct cannulation in each subgroup

	C group	**C+GW group**	**S group**	**S+GW group**
No. of patients	101	102	100	97
Excluded patient (s) *	1	4	3	5
Procedure started by operator expertise **				
Low/moderate/high	37/35/29	40/26/36	31/28/41	37/28/32
SBDC within 10 min	72 (71.3%)	75 (73.5%)	68 (68%)	67 (69.1%)
Time for SBDC within 10 min †				
Average, seconds ± SE	206 ± 173.1	172.8 ± 149.2	236.7 ± 206.8	176.2 ± 164.8
Fluoroscopic time for SBDC within 10 min †				
Average, seconds ± SE	57.5 ± 74.7	38.7 ± 56.7	62.7 ± 60.8	34.1 ± 66.0
Pancreatic opacification	52 (52%)	-	57 (58.8%)	-
Accidental pancreatic duct insertion	-	48 (47.5%)	-	50 (51.5%)
Use for precut	3 (3%)	4 (4.1%)	4 (4.1%)	2 (2.2%)
Final SBDC	95 (94.1%)	96 (94.1%)	95 (95%)	90 (92.8%)

SBDC, selective bile duct cannulation; C group, ERCP catheter with contrast medium/without guidewire (GW) group; C+GW group, ERCP catheter with GW /without contrast medium group; S group, sphincterotome with contrast medium/without GW group; S+GW group, sphincterotome with GW /without contrast medium group.

* One patient in the C group had ampullary neoplasm. Four patients in the C+GW group had multiple duodenal ulcers, anomalous pancreatico-biliary channel, Billroth II gastrectomy, and a duodenal papilla that could not be accessed endoscopically. Three patients in the S group had ampullary neoplasm, anomalous pancreatico-biliary channel, and a duodenal papilla that could not be accessed endoscopically. The duodenal papilla in all 5 patients in the S+GW group could not be accessed endoscopically.

** The 4 subgroups showed no significant difference in started by low/moderate/high ERCP experience. Operator expertise level was defined on the basis of the total career length as low if less than 4 years, moderate if 5–9 years, and high if more than 10 years.

† Calculated in successful cases alone.

Table 3-2. Results of methods of final selective bile duct cannulation over 10 min in each subgroup

	C group	**C+GW group**	**S group**	**S+GW group**
No. of failure of SBDC within 10 min	29	27	32	30
Final success of SBDC	23	21	27	23
Final SBDC technique				
C	7	3	1	3
C+GW	4	1	1	-
S	-	1	4	-
S+GW	1	1	5	8
Pancreatic GW *	9	9	13	10
Precut	2	5	3	2
Others	-	1 **	-	-

SBDC, selective bile duct cannulation; C (group), ERCP catheter with contrast medium/without guidewire (GW)(group); C+GW (group), ERCP catheter with GW/without contrast medium (group); S (group), sphincterotome with contrast medium/without GW (group); S+GW (group), sphincterotome with GW /without contrast medium (group).

* Included double GW technique.

** In the C+GW group, SBDC with the two-devices-in-one-channel method was successful in 1 patient.

Table 4. Complications in each of the study groups

	C group	**C+GW group**	**S group**	**S+GW group**
No. of patients	101	102	100	97
Pancreatic stent/naso-pancreatic drainage	13 (12.9%)	4 (3.9%)	7 (7%)	8 (8.2%)
Post-ERCP pancreatitis	4 (4%)	6 (5.9%)	2 (2%)	2 (2.1%)
Mild/moderate/severe	2/1/1	3/-/3	1/1/-	1/-/1
Hyperamylasemia	15 (14.9%)	20 (19.6%)	13 (13%)	19 (19.6%)
Ampulla of Vater perforation *	-	2	-	2

ERCP, endoscopic retrograde cholangiopancreatography; C group, ERCP catheter with contrast medium/without guidewire (GW) group; C+GW group, ERCP catheter with GW/without contrast medium group; S group, sphincterotome with contrast medium/without GW group; S+GW group, sphincterotome with GW/without contrast medium group.

* Ampulla of Vater perforations were caused by the GW passed through the posterior wall of the ampulla of Vater.

Table 5. Univariate and multivariate analyses to identify risk factors for failure of selective bile duct cannulation

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age		.819		
<70y	1.000			
≥70Y	0.940 (0.601-1.472)			
Gender		.289		
Male	1.000			
Female	0.780 (0.497-1.235)			
Method of cannulation		.782		
C	1.000			
C+GW	1.068 (0.689-1.654)			
S	0.816 (0.521-1.349)			
S+GW	1.034 (0.613-1.536)			
Underlying disease		.048		.289
Benign biliary disease	1.000		1.000	
Benign pancreatic disease	0.621 (0.274-1.406)		0.533 (0.161-1.769)	
Malignant biliary disease	1.136 (0.483-2.669)		1.068 (0.296-3.850)	
Malignant pancreatic disease	0.820 (0.355-1.890)		0.693 (0.206-2.331)	
Intradiverticular papilla		.721		
Without	1.000			
With	1.095 (0.762-1.573)			
Gallbladder		.066		.191

Without	1.000		1.000	
With	1.426 (1.012-2.009)		1.473 (0.825-2.632)	
Gallbladder stone		.047		.807
Without	1.000		1.000	
With	0.685 (0.477-0.984)		0.925 (0.496-1.726)	
Operator’s experience level		.045		.082
Low	1.000		1.000	
Moderate	1.367 (0.939-1.990)		1.412 (0.806-2.474)	
High	0.829 (0.541-1.272)		0.733 (0.415-1.294)	

OR, odds ratio; CI, confidence interval; C, ERCP catheter with contrast medium/without guidewire (GW); C+GW, ERCP catheter with GW/without contrast medium; S, sphincterotome with contrast medium/without GW; S+GW, sphincterotome with GW/without contrast medium

Table 6-1. Study characteristics and patient outcome between with- and without- guidewire, or between catheter and sphincterotome with regard to selective bile duct cannulation

Author (year)	RCT design	Cannula type	Setting	No. of endoscopists	No. of cases	SBDC limit	Primary SBDC success	Time to primary SBDC
Lella F (2004)	Non-cross over	S vs. S+GW	Single center	Single	200 vs. 200	None	195 (97.5%) vs. 197 (98.5%) (NS)	39 vs. 37 min (median) (NS)
Artifon E (2007)	Non-cross over	S vs. S+GW	Single center	Single	150 vs. 150	10 attempts	108 (72%) vs. 132 (88%) ($p < 0.001$)	n/a
Bailey AA (2008)	Non-cross over	S vs. S+GW	Single center	Two and fellows	211 vs. 202	10 min (5 min fellow)	156 (73.9%) vs. 167 (82.7%) ($p = 0.03$)	150 vs. 120 sec (median) (NS)
Katsinelos P (2008)	Cross over	C vs. C+GW	Single center	Single	165 vs. 167	10 min	89 (53.9%) vs. 136 (81.4%) ($p < 0.001$)	3.53 vs. 4.48 min (average) ($P = 0.04$)
Lee TH (2009)	Non-cross over	S vs. S+GW	Single center	Single	150 vs. 150	10 min or 5 PD entries	124 (82.7%) vs. 132 (88%) (NS)	n/a
Nambu (2010)	Cross over	C vs. S+GW	Single center	Multiple	86 vs. 86	10 min	62 (73.8%) vs. 67 (77.9%) (NS)	n/a
Currnet study	Cross over	C vs. C+GW vs. S vs. S+GW	Multicenter	Multiple	101 vs. 102 vs. 100 vs. 97	10 min	72 (71.3%) vs. 75 (73.5%) vs. 68 (68%) vs. 67 (69.1%) (NS)	206 vs. 172.8 vs. 236.7 vs. 176.2 sec (average) (NS)

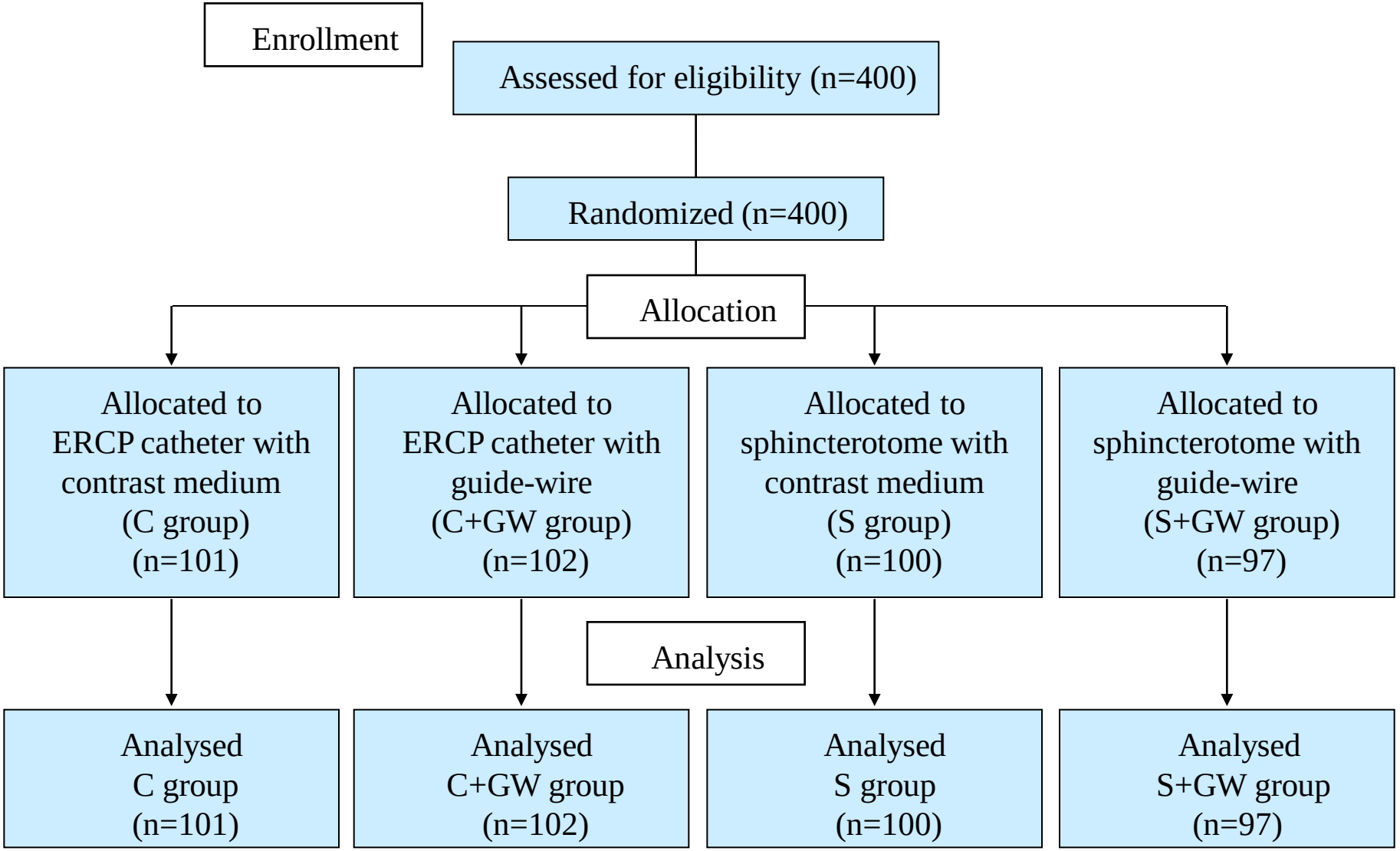
SBDC, selective bile duct cannulation; S, sphincterotome; GW, guidewire; min, minutes; n/a, data not available; NS, not significant; C, ERCP catheter; PD, pancreatic duct; NS, not significant; n/a, data not available

Table 6-2. Study characteristics and patients outcome between with- and without- guidewire, or between catheter and sphincterotome with regard to selective bile duct cannulation

Author (year)	Number of attempts for primary SBDC	Fluoroscopic time for primary SBDC	Use of precut	Final SBDC success	PEP	Angle of duodenoscope	GW size	Tip of the GW	GW controller
Lella F (2004)	4 vs. 4 (median) (NS)	n/a	0 vs. 0	195 (97.5%) vs. 197 (98.5%) (NS)	8 vs. 0 ($P < 0.01$)	5°	0.035	n/a	n/a
Artifon E (2007)	Details not reported ($P = 0.001$)	n/a	33 vs. 13 ($P = 0.007$)	141 (94%) vs. 145 (96.7%) (NS)	25 vs. 13 ($P = 0.037$)	5°	0.035	n/a	n/a
Bailey AA (2008)	Details not reported (NS)	n/a	29 vs. 25 (NS)	204 (96.7%) vs. 198 (98%) (NS)	13 vs. 16 (NS)	n/a	n/a	n/a	Assistant
Katsinelos P (2008)	3.09 vs. 3.81 (average) ($P = 0.02$)	n/a	31 vs. 25 (NS)	129 (78.2%) vs. 140 (83.8%) (NS)	13 vs. 9 (NS)	n/a	0.035	Straight-tipped	Assistant or endoscopist
Lee TH (2009)	n/a	n/a	36 vs. 28 (NS)	147 (98%) vs. 148 (98.7%) (NS)	17 vs. 3 ($P = 0.001$)	5°	0.035	n/a	Assistant
Nambu (2010)	n/a	n/a	4 vs. 3 (NS)	80 (95.2%) vs. 86 (100%)	5 vs. 2 (NS)	15°	0.035	Angle-tipped	n/a
Current study	3.3 vs. 3.3 vs. 3.4 vs. 3.3 (average) (NS)	57.5 vs. 38.7 vs. 62.7 vs. 34.1 sec * (average)	3 vs. 4 vs. 4 vs. 2 (NS)	95 (94.1%) vs. 96 (94.1%) vs. 95 (95%) vs. 90 (92.8%) (NS)	4 vs. 6 vs. 2 vs. 2 (NS)	15°	0.035	Straight-tipped	Assistant

SBDC, selective bile duct cannulation; PEP, post-ERCP pancreatitis; GW, guidewire; NS, not significant; n/a, data not available

* The time in the with-GW group (median, 15 sec) was significantly shorter than that in the without-GW group (median 36 sec; $P = 0.00004$). Of the 4 subgroups, the S group had a significantly longer fluoroscopy time than either the C+GW or S+GW groups ($P < 0.05$).


Enrollment
Assessed for eligibility (n=400)
Randomized (n=400)
Allocation
Allocated to ERCP catheter with contrast medium (C group) (n=101)
Allocated to ERCP catheter with guide-wire (C+GW group) (n=102)
Allocated to sphincterotome with contrast medium (S group) (n=100)
Allocated to sphincterotome with guide-wire (S+GW group) (n=97)
Analysis
Analysed C group (n=101)
Analysed C+GW group (n=102)
Analysed S group (n=100)
Analysed S+GW group (n=97)