A prospective randomized controlled multicenter trial of duodenoscopes with 5° and 15° backward-oblique angle using wire-guided cannulation: effects on selective cannulation of the common bile duct in endoscopic retrograde cholangiopancreatography

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Short title: RCT of duodenoscopes using WGC

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ABSTRACT

Background. In duodenoscopy during endoscopic retrograde cholangiopancreatography (ERCP), a backward-oblique angle duodenoscope (BOAD) is generally used. In Japan, 15° BOAD are mainly used, but in Western countries, 5° BOAD are mostly used. In bile duct cannulation associated with ERCP, a catheter for contrast imaging is used in Japan, but wire-guided cannulation (WGC) using a papillotome is standard in Western countries. We conducted a randomized controlled multicenter trial to evaluate the contributions of different duodenoscopes using WGC to selective common bile duct cannulation.

Methods. Subjects comprised 179 consecutive patients who underwent ERCP. Patients were randomized into the 15° BOAD group (15° group, n=90) or the 5° BOAD group (5° group, n=89).

Results. The duodenal papilla could not be accessed endoscopically in two cases from each group. Success rates for bile duct cannulation by WGC without bow-up for the 15° and 5° groups were 85.6% and 56.2%, respectively (p<0.01). Success rates for bile duct cannulation by WGC with bow-up for the 15° and 5° groups were 88.9% and 78.7%, respectively. Total rates of bile duct cannulation for the 15° and 5° groups were 94.4% and 92.1%, respectively. As for accidents, incidences of acute pancreatitis for the 15° and 5° groups were 5.6% and 9.0%, respectively, with no significant difference seen.

Conclusions. With 15° BOAD, bile duct cannulation was favorable without papillotome bow-up. With 5° BOAD, the success rate of WGC may be improved by adjusting the angle based on papillotome bow-up.

Key words:

endoscopic retrograde cholangiopancreatography (ERCP), backward oblique-viewing endoscope, wire-guided cannulation, selective cannulation of the common bile duct, randomized controlled multicenter trial (RCT)

Abbreviations:

ERCP, Endoscopic retrograde cholangiopancreatography

BOAD, Backward-oblique angle duodenoscope

WGC, Wire-guided cannulation

ITT, Intention-to-treat

PP, Per protocol

CBD, Common bile duct

Introduction

Despite recent advances in noninvasive diagnostic imaging techniques such as ultrasonography, computed tomography and magnetic resonance image, endoscopic retrograde cholangiopancreatography (ERCP) using a duodenoscope can yield valuable information that cannot be gathered using conventional modalities, and remains essential for the diagnosis and treatment of bile duct and pancreatic diseases.

In general, backward-oblique angle duodenoscopes (BOADs) are used for ERCP. In Japan, 15° BOADs are mainly used, whereas Western countries favor 5° BOADs. This explains why a catheter for contrast imaging is used for bile duct cannulation during ERCP in Japan, while a papillotome as used for endoscopic papillary sphincterotomy is often used in Western countries. Furthermore, in recent years, cannulation methods using not only a papillotome, but also a guidewire have been recommended in Western countries [1-5]. Compared to catheters for contrast imaging, one advantage of using a papillotome lies in the ability to adjust angles by bow-up, and one advantage of using a guidewire is the reduced likelihood of contrast agent accidentally entering the bile duct, thus theoretically lowering the incidence of acute pancreatitis [2]. A papillotome is not generally used for bile duct cannulation during ERCP in Japan, for a variety of reasons. One major reason is probably the cost compared with a conventional catheter. Use of a papillotome may improve the success rate for selective biliary cannulation during ERCP compared to conventional catheters for contrast imaging techniques. Therefore, in Japan, wire-guided cannulation (WGC) using a papillotome is expected to be more important in the future. However, the effects of endoscope viewing angle on bile duct cannulation have not been clarified.

The present study clarified differences in success rates for bile duct cannulation in relation to endoscope viewing angles and papillotome angle adjustment.

Methods

This randomized controlled multicenter trial was performed between September and December 2008 at seven large endoscopic units each performing more than 300 ERCPs annually.

Katsinelos et al. reported success rates for selective biliary cannulation using a conventional catheter were 53.9-81.4% [4], while Maydeo et al. reported rates of 93-95% for selective biliary cannulation using WGC [6]. Given these results, the sample size calculation for the present study was based on the assumption of an 80% success rate for biliary cannulation with a papillotome and a 95% success rate with WGC. More than 76 patients in each study group was thus needed using a 5% significance level and a statistical power of 80% in a two-sided equivalence test. More than 170 patients were enrolled, as around 10% of subjects were expected to be lost due to the inclusion and exclusion criteria and follow-up.

The study group included patients who required cholangiography and an intact papilla of Vater. Exclusion criteria were as follows: age 20 years younger; performance status of 4 (“Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair”); history of previous endoscopic sphincterotomy; previous endoscopic balloon dilatation; ampullary neoplasm and infiltration of the papillary area by pancreatic cancer; acute pancreatitis; chronic pancreatitis with an acute exacerbation; impacted common bile duct

stone; Billroth II gastrectomy; Roux-en-Y reconstruction; separate orifices of the common bile duct and pancreatic duct on the papilla; pancreaticobiliary maljunction; pregnancy; or refusal to provide informed consent.

Randomization of patients was performed when the patients required ERCP, using the envelope method just before the procedure.

ERCP was performed using a BOAD with an elevator function (TJF-260V or TJF-240; Olympus, Tokyo, Japan). Backward viewing angle was 15° for TJF-260V and 5° for TJF-240. In particular, the TJF-260V had a mechanism for increased angle of articulation in compared with 5° BOAD (Table 1). A CleverCut3V (Olympus) with a tip length of 7 mm and a knife length of 25 mm was used as a papillotome. As a guidewire, a 0.035-inch hard guidewire (stiff-type Jagwire; Boston Scientific Japan, Tokyo, Japan) or 0.035-inch hard guidewire (Revowave; Olympus) was used.

All endoscopic procedures were performed by physicians with ≥10 years of experience with ERCP. All endoscopic procedures were performed with the patient under conscious sedation using intravenous pethidine hydrochloride and diazepam.

With regard to bile duct cannulation, WGC using a papillotome was performed as follows. A papillotome preloaded with a guidewire was inserted into the working channel of the duodenoscope. After viewing the duodenal papilla from the front, time measurement was started when bile duct cannulation was attempted. From either outside the orifice of the duodenal papilla or inside the orifice, the guidewire was gently and carefully advanced under the guidance of X-ray fluoroscopy and inserted into the bile duct. A guidewire that could not be inserted into the bile duct was retracted and then another attempt was made

at insertion. After inserting the guidewire into the bile duct, the papillotome was inserted deep into the bile duct along the guidewire. Bile duct cannulation was checked by visually confirming bile or performing cholangiography to confirm the bile duct. With regard to WGC techniques, use of contrast agent was banned until the bile duct was cannulated.

In each group, bile duct cannulation was started using a papillotome. A papillotome without bow-up was used to resemble a conventional catheter with a time limit of 10 min (Step 1: WGC without bow-up). If the bile duct could not be cannulated in Step 1, angles were adjusted by papillotome bow-up for bile duct cannulation with a time limit of 10 min (Step 2: WGC with bow-up). If cannulation was not possible with Steps 1 or 2 (10 min each, for a total of 20 min), then no restrictions were placed on centers and endoscopists afterwards. In addition, no restrictions were placed on the use of contrast agents. At the end of the test, all procedures used for cannulation were recorded.

After ERCP-related procedures, 50,000 units of urinastatin were drip-infused twice (day of surgery and the next morning) over a period of 1-2 h. Through a side tube, antibiotic agent was drip-infused twice (once after ERCP-related procedures and once the next morning).

The following items were investigated for each step (Steps 1 and 2), respectively: 1) success rate of bile duct cannulation, 2) time for bile duct cannulation, 3) number of attempts for bile duct cannulation, 4) number of accidental pancreatic duct insertions, and 5) accidents. Accidents were classified using the Cotton classification [7]. Based on the consensus meeting held in 1991, the diagnostic criteria for post-ERCP pancreatitis were abdominal pain lasting >24 h after ERCP and hyperamylasemia (>3 times

the upper limit of the normal range). The Cotton classification was used for assessment of severity, but based on the medical circumstances in Japan, the time for food consumption was used rather than the duration of hospitalization. The other techniques followed the original method.

Intention-to-treat (ITT) and per protocol (PP) methods were used in this analysis. ITT analysis was based on the original total cohort of patients enrolled. PP analysis was based on the subset of patients in whom selective common bile duct (CBD) cannulation was successful. Rates of successful biliary cannulation and complications were evaluated by ITT analysis. The time to selective CBD cannulation, number of attempts for selective CBD cannulation and accidental pancreatic duct insertion were evaluated by PP analysis.

Statistical analysis

Statistical analysis was performed using SPSS II for Windows, version 8.0.1 J (SPSS, Chicago, Illinois, USA). For comparison of the rates of selective cannulation of the common bile duct, time to selective common bile duct cannulation, numbers of attempts for selective cannulation of common bile duct cannulation, accidental pancreatic duct insertion, and complications were used. Statistical analysis was performed using the χ^2 or Fisher's exact test for comparisons between group. Values of $P<0.05$ were considered statistically significant. As for post-ERCP pancreatitis, after extracting arbitrary risk factors, variables were selected by multivariate analysis based on logistic regression analysis using the step-up method.

Results

A total of 179 consecutive patients underwent ERCP with a median of 17 patients (range, 7-56 patients) in each institution. Patients were randomized into the 15° BOAD group (15° group, n=90) or the 5° BOAD group (5° group, n=89) (Figure 2). The duodenal papilla could not be accessed endoscopically in two cases from each group.

Baseline patient characteristics

Between the 15° and 5° groups, no significant differences existed in age, gender or presence of periampullary diverticulum. With regard to underlying diseases, choledocholelithiasis was most common, but no significant differences existed in all diseases between groups. Furthermore, no significant differences existed in tests or treatments following bile duct cannulation between groups (Table 2).

Selective cannulation of the common bile duct

Table 5 compares the results for Step 1 (WGC without bow-up) and Step 2 (WGC with bow-up) between the two groups.

With Step 1, the success rate of bile duct cannulation for the 15° group was 85.6%, significantly higher than the 56.2% for the 5° group (P<0.01). Median time for cannulation was 90 s for both groups. The median number of attempts for bile duct cannulation was two for both groups. The median number of accidental pancreatic duct insertions was 0 for the 15° group and 1 for the 5° group.

With Step 2 (subsequently using bow-up), success rate of bile duct cannulation

for the 15° and 5° groups was increased to 88.9% and 78.7%, respectively. With Step 2, median time for cannulation for the 15° and 5° groups was 145 and 100 s, respectively, but no significant difference was seen between groups. The median number of attempts for bile duct cannulation for the 15° and 5° groups was 3 and 1, respectively. The median number of accidental pancreatic duct insertions for the 15° and 5° groups was 0 and 1, respectively.

Figure 3 shows the summary of results of the study groups. The success rate of bile duct cannulation for the 15° and 5° groups was 85.6% and 56.2%, respectively. In both groups, with adjustment of angles by knife bow-up and WGC, the success rate of bile duct cannulation was improved synergistically. In particular, synergistic effects of about 22% were obtained for the 5° group. The final success rate of bile duct cannulation (Steps 1 and 2 and other procedures) for the 15° and 5° groups was 94.4% and 92.1%, respectively. Bile duct cannulation was not possible by WGC (Step 1) or WGC with bow-up (Step 2) in eight patients in the 15° group and 17 patients in the 5° group. With the subsequent cannulation methods, cannulation was possible in five patients in the 15° group and 12 patients in the 5° group. In all five patients in the 15° group, the pancreatic duct guidewire method was employed, and Precut was performed on two patients (data not shown). Also, the pancreatic duct guidewire method was employed on 11 of the 17 patients in the 5° group, and Precut was performed on three patients (including overlaps). Cannulation was not possible with any procedure in three patients from the 15° group (3.3%) and five patients from the 5° group (5.6%).

Complications

In terms of accidents, post-ERCP acute pancreatitis was seen in five patients in

the 15° group (5.6%: mild, n=3; moderate, n=2) and eight patients in the 5° group (9.0%: mild, n=4; moderate, n=4), and no significant difference was seen between the two groups. Incidence of hyperamylasemia for the 15° and 5° groups was 14.4% and 19.1%, respectively, and no significant difference existed between the two groups. For the 15° group, Mallory-Weiss syndrome was seen in 1 patient, but the patient responded to conservative therapy. Also, no severe complications were seen (Table 5). Although post-ERCP pancreatitis was seen even with WGC, severe acute pancreatitis was not seen. The following 17 risk factors for acute pancreatitis were extracted and subjected to multivariate analysis: age; gender; duodenoscope used; intradiverticular papilla; endoscopic sphincterotomy; endoscopic papillary balloon dilatation; endoscopic biliary drainage; intraductal ultrasound; bile duct biopsy; pancreatic duct biopsy; WGC success/failure; ≥5 min of WGC procedure without bow-up (Step 1); ≥5 min of WGC procedure with bow-up (Step 2); accidental pancreatic duct insertion during WGC; pancreatography; pancreatic duct guidewire placement; precut; and pancreatic duct stent placement. No significant risk factors were extracted (data not shown).

Discussion

With WGC, angles can be adjusted by papillotome bow-up, and when compared to catheters for contrast imaging, bile duct cannulation is easier [1-5]. To confirm the significance of angle adjustment by a papillotome knife, we investigated cannulation rates before and after angle adjustment. With regard to selective bile duct cannulation by WGC in the present study, the success rate of bile duct cannulation was high using the 15° BOAD

without papillotome bow-up. Also, when using the 5° BOAD, the success rate of bile duct cannulation was low without papillotome bow-up. Subsequently, without papillotome bow-up (or in other words, with a catheter for contrast imaging), using a 15° BOAD is more advantageous for bile duct cannulation compared with 5° BOAD. The reason for the low success rate of bile duct cannulation for the 5° group could have been that the difference in viewing angles, the angle between scope and catheter using elevator function and raising devices made it difficult to aim upwards without papillotome bow-up. However, if angles could be adjusted by papillotome bow-up, success rates of bile duct cannulation were similar between the two groups, and results were comparable with those in past reports [1-5]. These findings suggest that compared to the 5° duodenoscope, the 15° duodenoscope is more useful for bile duct cannulation, and using WGC with the 15° duodenoscope may synergistically increase the success rate of cannulation. Conversely, with the 5° duodenoscope, the success rate of cannulation can be increased synergistically with papillotome bow-up, and this is a reasonable for bile duct cannulation.

In Japan, bile duct cannulation is traditionally performed using a 15° BOAD and a catheter for contrast imaging, and because a relatively high rate of bile duct cannulation can be achieved using this method, whether WGC using a papillotome will be performed more often in the future is unclear. However, according to the present results, the success rate of cannulation improved about 3% by adjusting the angle of the papillotome knife (bow-up), thus clarifying that WGC is highly valuable. On the other hand, with a 5° BOAD, using a papillotome is very reasonable, and this explains the current situation in Western countries. The success rate of cannulation improved over 20% by adjusting the angle of the

papillotome knife (bow-up) using a 5° BOAD.

In Western countries, 15° BOADs are not commercially available. In the future, we hope that the success rate of bile duct cannulation in Western countries will improve as 15° BOADs gain popularity. Using 5° BOADs, the papillotome with bow-up may be needed to make adjustments to the bile duct. However, using with 15° BOADs, a conventional catheter may be sufficient. The present results suggest the significance of the effects of endoscope viewing angle using elevator function on selective bile duct cannulation.

Limitations in this study were that the participating centers may not have been accustomed to the endoscopic equipment, as they do not often handle 5° BOAD. If all endoscopists used 5° BOAD routinely, the success rates for bile duct cannulation by 5° BOAD using WGC may be increased compared to the present results. Weakness of this study was not a double-blinded manner.

With regard to accidents, no significant differences in post-ERCP pancreatitis were seen based on the viewing angle of duodenoscopes. The incidence of post-ERCP pancreatitis may be able to be reduced by WGC, but in the future, studies will be needed to compare catheters for contrast imaging and bile duct cannulation by WGC in Japan and subsequently investigate not only bile duct cannulation, but also the incidence of post-ERCP pancreatitis.

Conclusion

Compared to the 5° duodenoscope, the 15° duodenoscope is superior even without papillotome bow-up. The success rate of cannulation may also be improved by WGC.

Using the 5° duodenoscope, WGC may be reasonably performed using a papillotome.

Appendix

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Conflict of interest statement

We declare that we have no conflict of interest.

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Figure Legends

Figure 1: Endoscopic view of duodenoscope

a) Endoscopic view with 15° backward-oblique angle. b) Endoscopic view with 5° backward-oblique angle.

We obtained a broader view with a 15° backward-oblique angle duodenoscope than with a 5° backward-oblique angle duodenoscope.

Figure 2: Flow diagram for study participants

Figure 3: Summary of results for the study groups

Table 1. Duodenoscope specifications

	TJF-240	TJF-260V
Backward-oblique angle	5°	15°
Outer diameter (mm)	13.5	13.5
Working channel inner diameter (mm)	4.2	4.2
Angles between scope and catheter		
using elevator function	90°	115°

Table 2. Baseline patient characteristics

	15° group (n=90)	5° group (n=89)
Median age (range)	67 (25-94)	70 (40-92)
Gender		
Male	60	48
Female	30	39
Periampullary diverticulum	26 (28.9%)	20 (22.5%)

Choledocholithiasis	42 (46.7%)	40 (45%)
Cholangiocarcinoma	11 (12.7%)	10 (11.2%)
Pancreas cancer	10	9
Gallbladder carcinoma	3	6
Cholangiocellular carcinoma	3	3
Other benign diseases	14	15
Other malignant diseases	7	4

Table 3. Endoscopic procedures

	15° group (n=90)*	5° group (n=89)*
EST	40 (45.6%)	33 (37.9%)
EPBD	3 (3.3%)	1 (1.1%)
EBD (ENBD, EBS)	45 (50%)	47 (52.8%)
with EST	20	16
IDUS	27 (30%)	28 (31.5%)
Bile duct	26	27
Pancreatic duct	1	1

Aspiration, brush, biopsy	27 (30%)	28 (31.5%)
Bile duct	18	25
Pancreatic duct	9	3

EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation; EBD; endoscopic biliary drainage; ENBD, endoscopic nasobiliary drainage; EBS, endoscopic biliary stenting; IDUS, intraductal ultrasonography.

*The duodenal papilla could not be accessed endoscopically in two cases from each group.

Table 4. Cannulation results

	15° group (n=90)*	5° group (n=89)*
Step 1 (WGC without bow-up)		
Selective CBD cannulation success rate	85.6% (77/90)**	56.2% (50/89)
Time to selective CBD cannulation***		
sec, median (range)	90 (3-523)	90 (10-583)
Number of attempts for selective CBD cannulation***		
median (range)	2 (1-12)	2 (1-18)
Accidental pancreatic duct insertion		
median (range)	0 (1-18)	1 (0-8)

Step 2 (WGC with bow-up)		
Selective CBD cannulation success rate	23.1% (3/13)	51.3% (20/39)
Time to selective CBD cannulation***		
s, median (range)	145 (20-590)	100 (10-590)
Number of attempts for selective CBD cannulation***		
median (range)	3 (2-11)	1 (1-5)
Accidental pancreatic duct insertion		
median (range)	0 (0-10)	0 (0-2)

WGC, wire-guided cannulation; CBD, common bile duct

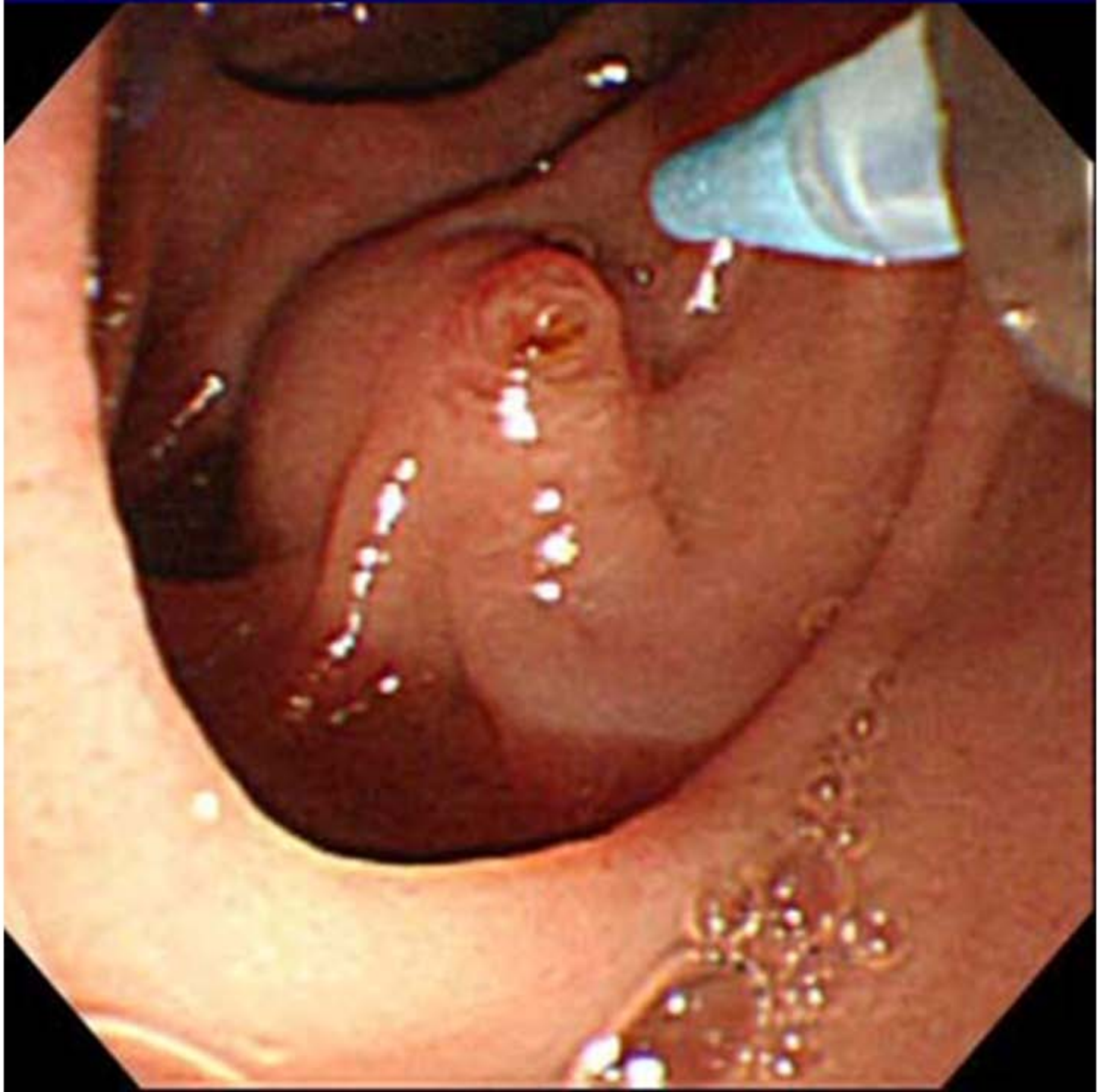
* The duodenal papilla could not be accessed endoscopically in two cases from each group. ** $P<0.01$.

*** Calculated in successful cases alone.

Table 5. Post-ERCP complications of the study groups

	15° group (n=90)	5° group (n=89)
Acute pancreatitis	5 (5.6%)	8 (9.0%)
Mild	3	4
Moderate	2	4
Hyperamylasemia	13 (14.4%)	17 (19.1%)
Hemorrhage	0	0
Perforation	0	0
Other	1*	0

* Mallory-Weiss syndrome



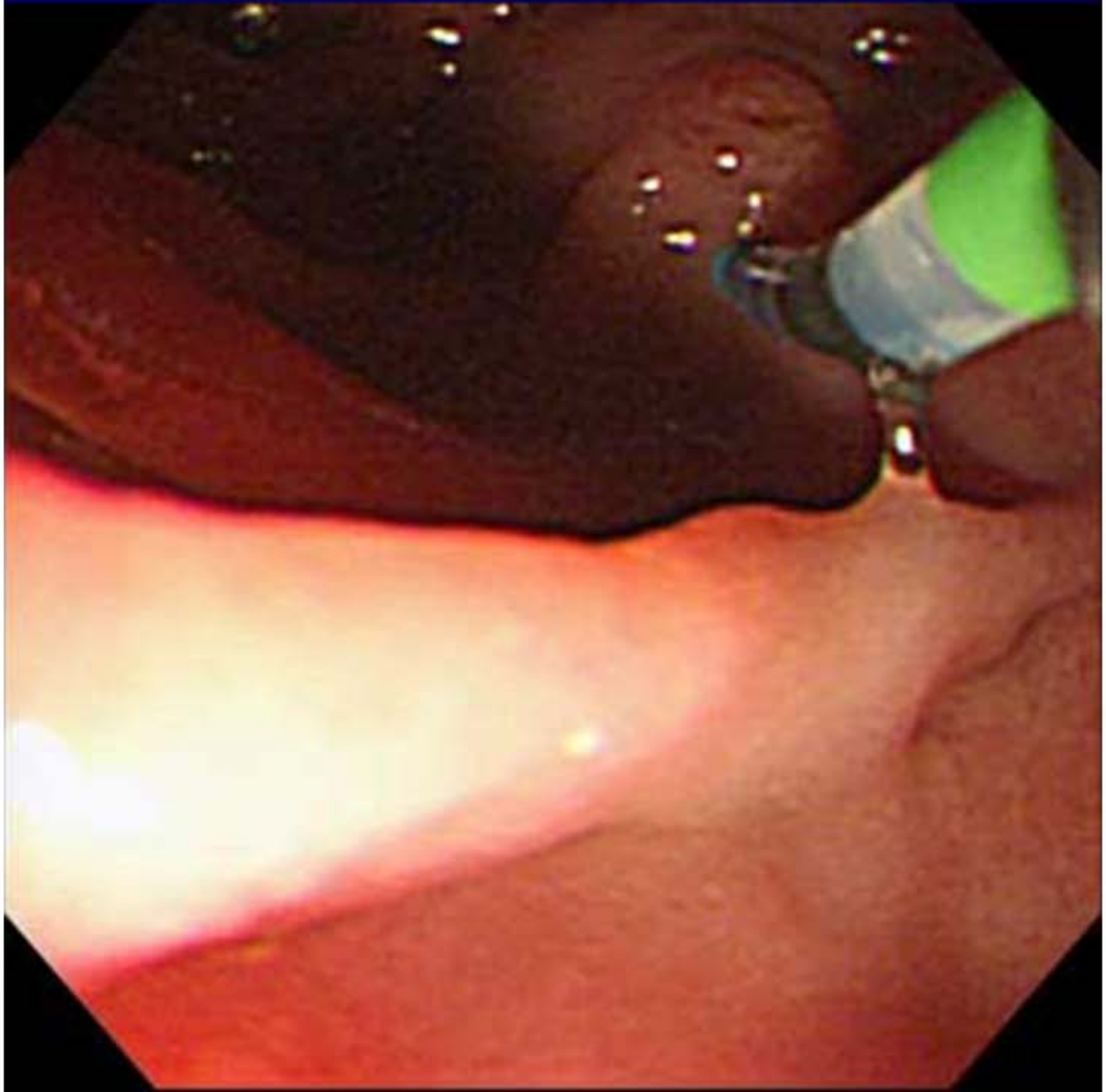
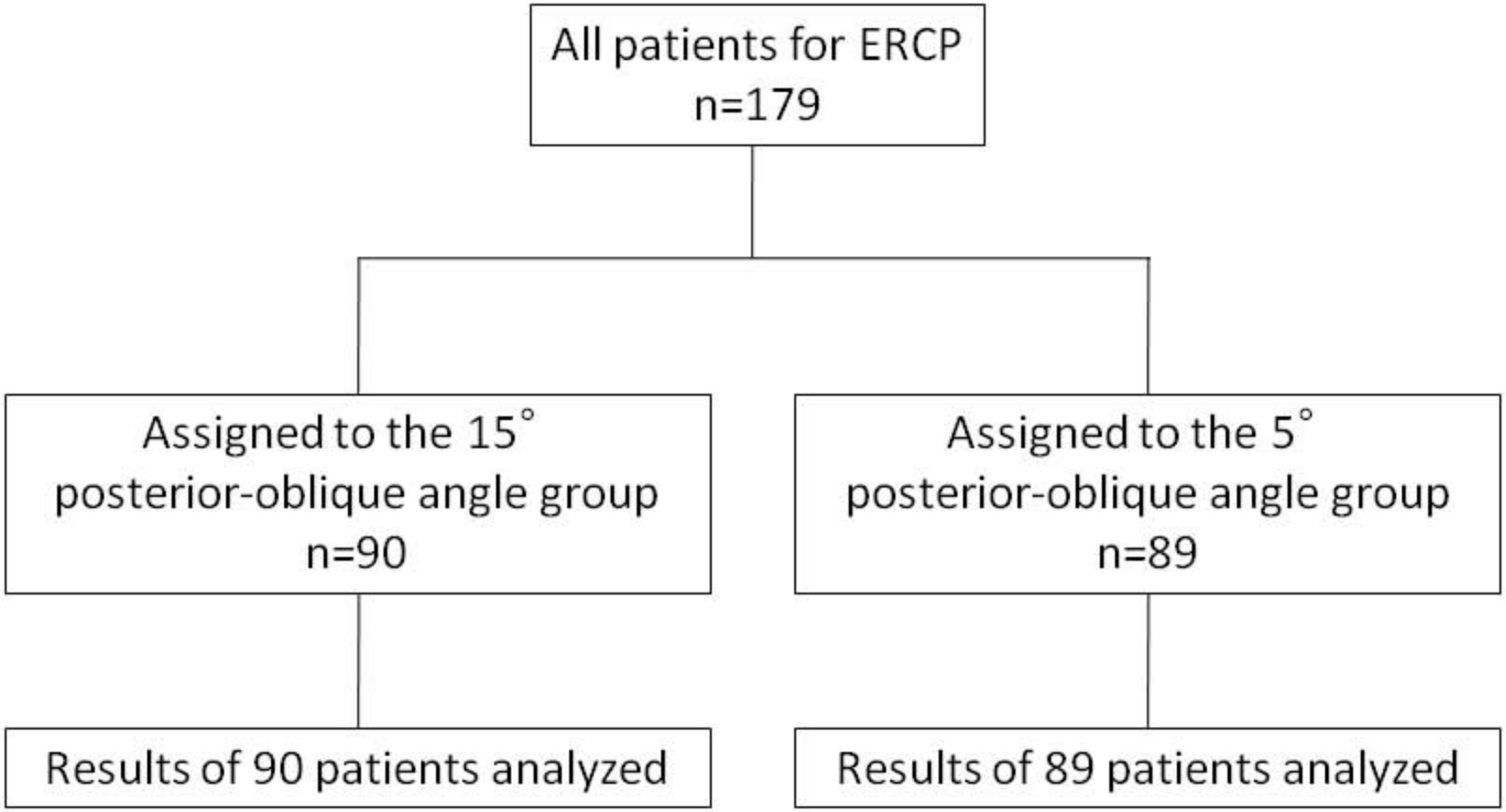
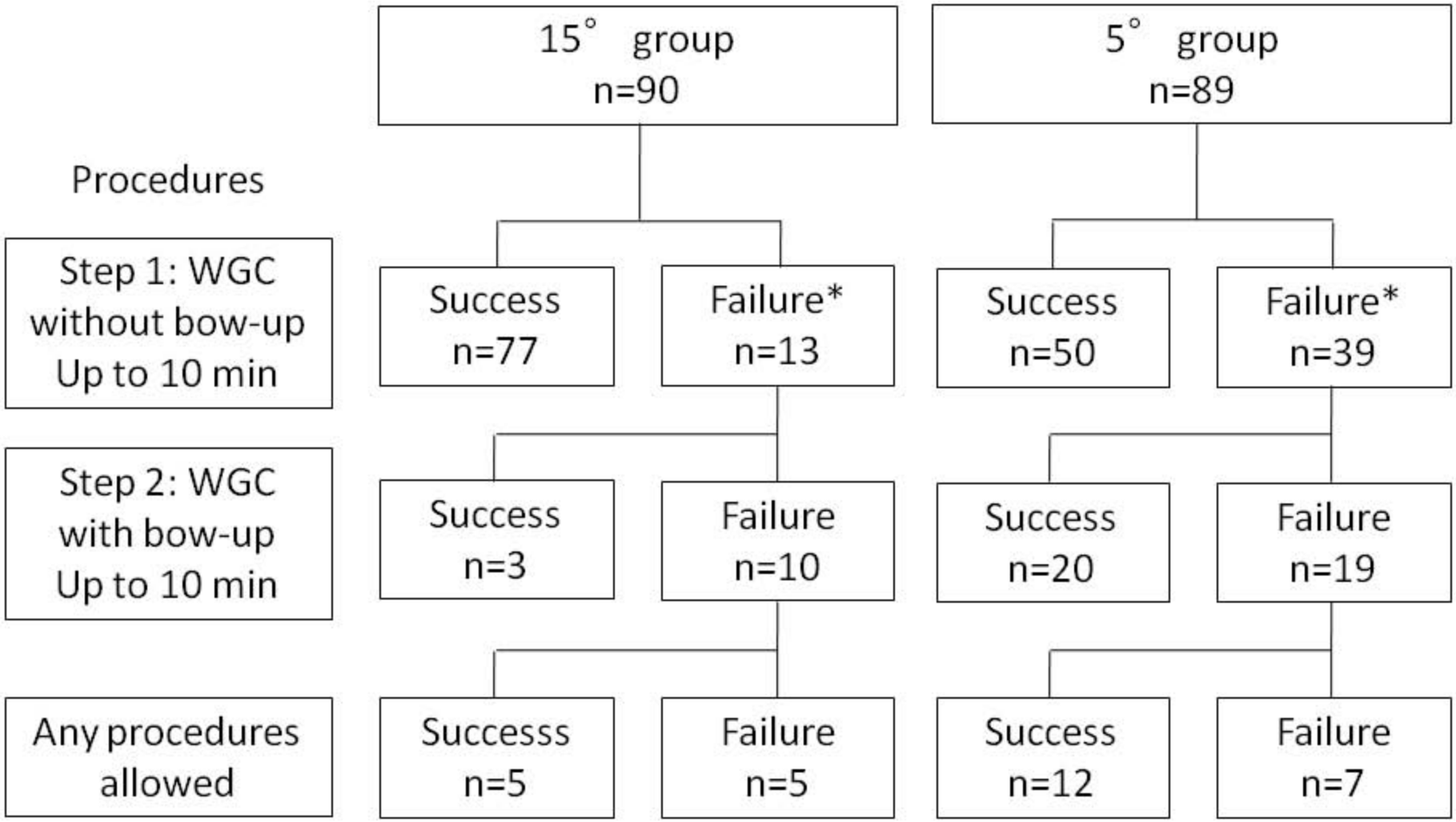


Figure 2. Flow diagram of the participants in the study



ERCP; endoscopic retrograde cholangiopancreatography

Figure 3. Summary of results of the study groups



WGC; wire-guided cannulation

*The duodenal papilla could not be accessed endoscopically in two cases.