



A multicenter randomized trial comparing the use of touch versus no-touch guidewire technique for deep biliary cannulation: the TNT study

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Background and Aims: There are 2 techniques described for selective bile duct guidewire cannulation, the touch (T) technique (engaging the papilla with a sphincterotome and then advancing the guidewire) and the no-touch (NT) technique (engaging the papilla only with the guidewire). The aim of this prospective, multicenter randomized study was to compare the outcomes of the 2 guidewire cannulation techniques.

Methods: Three hundred consecutive patients with naïve papillae were enrolled in 2 groups (150 to T group and 150 to NT group). A maximum of 15 biliary cannulation attempts, for no longer than 5 minutes, or a maximum of 5 unintentional cannulations of the pancreatic duct for each group were performed. If biliary cannulation failed, the patient was crossed over to the other technique with the same parameters. The primary outcome was the guidewire cannulation success rate using either the T or NT technique. Secondary outcomes were the number of attempts and cannulation duration, number of pancreatic duct cannulations, and adverse events.

Results: The primary cannulation rate was significantly higher in the T group compared with the NT group (88% vs 54%, $P < .001$), and the cannulation rate was significantly higher using the T technique compared with the NT technique also after crossover (77% vs 17%, $P < .001$). The mean number of cannulation attempts was 4.6 in the T group versus 5.5 in the NT group ($P = .006$), and the duration of cannulation before crossover ($P < .001$) and overall cannulation duration after crossover ($P < .001$) were significantly lower in the T group. The number of unintended pancreatic duct cannulations was statistically higher using the T technique compared with the NT technique ($P = .037$). The rates of adverse events did not significantly differ between the 2 groups.

Conclusions: Our results clearly indicated that the T technique is superior to the NT technique for biliary cannulation. (Clinical trial registration number: NCT01954602.) (Gastrointest Endosc 2018;87:196-201.)

Selective deep cannulation of the common bile duct (CBD) is required for successful therapeutic procedures during ERCP. However, cannulation of the papilla can be a technical challenge, even in experienced hands, and the success rate ranges from 50% to 90%.¹ The most popular techniques used in these circumstances are the

contrast-assisted cannulation technique and guidewire cannulation (GWC) technique.²⁻⁵

Currently, the GWC technique, introduced by Siegel and Pullano in 1987,⁶ is increasingly used as a primary cannulation technique because evidence shows that when compared with the contrast-assisted cannulation

Abbreviations: CBD, common bile duct; GW, guidewire; GWC, guidewire cannulation; NT, no-touch; PD, pancreatic duct; PEP, post-ERCP pancreatitis; RCT, randomized controlled trial; T, touch.

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technique, it is associated with a higher incidence of successful cannulation and reduced risk of adverse events, including post-ERCP pancreatitis (PEP).¹ Caution should be used when deciding on the appropriateness of the GWC technique because adverse events can occur, such as intramural dissection, pancreatic duct (PD) perforation, and the creation of false passages.

A prolonged attempt at GWC and papillary manipulation increases the risk of adverse events.^{7,8} The 2 basic GWC techniques for CBD cannulation are engaging the papillary orifice with a sphincterotome and then advancing the guidewire (GW) under fluoroscopic control (the touch [T] technique)⁹⁻¹² or advancing the GW 1 to 2 mm beyond the tip of the sphincterotome and directly inserting it into the papillary orifice in the CBD axis under fluoroscopic control (the no-touch [NT] technique).¹³⁻¹⁶ However, despite the existence of an increasing quantity of evidence in regard to these 2 approaches, there is no consensus as to which one is the most appropriate for the GWC procedure. Currently, there are no studies that compare the 2 different variants of the GWC technique. The aim of this randomized controlled trial (RCT) is to investigate whether clinical differences can influence the success rate of selective bile duct cannulation and the incidence of adverse events during GWC using the T or NT techniques.

METHODS

Study design

Between November 2013 and March 2015 a prospective RCT was carried out at 3 Italian tertiary endoscopy referral centers. A total of 6 endoscopists who had ERCP experience of more than 1000 cases and who each performed more than 150 procedures per year were involved in this study. All endoscopists used both GW methods to cannulate the CBD, but 3 preferred to use the T technique as the primary cannulation approach, whereas 3 preferred the NT technique.

The study protocol was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki and the ethics committees of the hospitals that approved the study protocol. The study was registered at clinicaltrials.gov (Clinical trial registration number: NCT01954602; protocol registration receipt: September 27, 2013; study start date: November 4, 2013). All patients provided written informed consent to take part in the study and were blinded from allocation.

Eligibility criteria

All consecutive patients 18 years of age or older with a pancreaticobiliary disease involving a naïve papilla referred for ERCP were considered for inclusion and were invited to take part in the study protocol. Exclusion criteria were the following: previous endoscopic sphincterotomy, previous endoscopic balloon dilation, presence of a previously

placed plastic or metal biliary stent, presence of an esophageal or gastro/duodenal stent, presence of a diverticular papilla, presence of a duodenal stenosis, ampullary neoplasm, infiltration of the papillary area by pancreatic cancer or cholangiocarcinoma, Billroth II gastrectomy or Roux-en-Y reconstruction, separate papillary orifices of the CBD and PD, anomalous pancreaticobiliary channel, patients unsuitable for endoscopic procedures because of contraindications, hemodynamic instability, a platelet count < 50,000/mm³, an international normalized ratio greater than 1.5 times the upper limit of normal, pregnancy, and refusal to provide informed consent.

Randomization

After the patients agreed to participate, they were randomized into either the T group or the NT group. Randomization was carried out using a computer-generated list. Assignments were prepared with a 1:1 ratio, and allocation was concealed using an opaque envelope system. Data from consecutive patients were prospectively collected through a standardized case report form and centralized at a coordinating analysis and interpretation center.

Procedure and study protocol

All procedures were performed with a large-channel duodenoscope, with anesthesiologist-assisted propofol sedation. A triple-lumen sphincterotome (Ultratome; Boston Scientific, Natick, Mass) and a 450-cm, .035-inch straight GW with a hydrophilic tip (Hydrajawire; Boston Scientific), operated by the physician, were used for cannulation and sphincterotomies.

In the T group the sphincterotome, preloaded with a GW, was oriented from the 11 to the 12 o'clock position on the papilla and bent to align it correctly with the bile duct axis. After a minimal insertion (1-3 mm) of the sphincterotome across the ampulla, the GW was carefully advanced through the CBD under fluoroscopy control until it was seen entering the bile duct. If unintended PD cannulation occurred, the GW was withdrawn and attempts made to redirect it toward the CBD. The maximum number of attempts was 15, with a duration of no longer than 5 minutes, or a maximum of 5 unintentional cannulations of the PD. If biliary cannulation was achieved by means of GW insertion, contrast medium was injected, whereas in the event of failure, the patient was crossed over to the other technique for a maximum period of 5 additional minutes or an additional 15 attempts or for a maximum of 5 additional unintentional cannulations of the main PD.

In the NT group the GW was advanced through a sphincterotome to approximately 1 to 3 mm beyond its tip and was then oriented to be correctly aligned with the CBD axis at the papilla orifice. Next, the tip of the GW was inserted into the ampulla and advanced gently under fluoroscopy so as to enter the CBD. If the GW entered

the PD, it was withdrawn and attempts made to redirect it toward the CBD.

After 5 minutes or 15 unsuccessful attempts or up to 5 unintentional cannulations of the PD, the patient was crossed over to the other technique for a maximum duration of 5 additional minutes, or an additional 15 attempts, or for a maximum of 5 additional unintentional cannulations of the main PD. When cannulation failed using both techniques, alternative techniques to access the biliary tree were adopted, such as needle-knife sphincterotomy, transpancreatic papillary septotomy, or double-wire cannulation, depending on the endoscopist's experience and preferred technique. None of the patients received nonsteroidal anti-inflammatory drugs or a prophylactic pancreatic stent.

Definition of events

Primary CBD cannulation success was defined as CBD cannulation with either of the 2 techniques (T or NT). The additional cannulation rates after crossover were also included in our analysis. Overall, final CBD cannulation success was defined as the sum of primary cannulation, crossover, and after-use of rescue techniques. The time needed for primary biliary cannulation was defined as the time period from the initial attempt at biliary cannulation to successful selective insertion of the sphincterotome into the CBD.

The starting point for measuring the time period for primary successful cannulation was when the sphincterotome or the GW first touched the papilla. Primary cannulation was considered to have failed when the GW was inserted into an undesired duct or false tract or slipped out. Cannulation time at crossover was defined as the total time elapsed from the initial attempt at biliary cannulation to successful selective insertion of the sphincterotome into the CBD at crossover. A crossover cannulation was considered a failure when the GW was inserted into an undesired duct or false tract or slipped out.

Consensus guidelines were used for definitions, grading, and therapy for ERCP adverse events.^{17,18} For procedure-related pancreatitis, a diagnosis of PEP was made if there was the typical abdominal pain associated with a greater than 3-fold elevation above the normal upper limit of serum amylase on day 1 after the procedure. The severity of pancreatitis was defined as the following: mild (2-3 days of hospitalization was required), moderate (4-10 days of hospitalization was necessary), or severe (10 or more days of hospitalization was required or if admission to the intensive care unit and/or a procedure [endoscopic, percutaneous drainage, or surgery] was necessary).

The severity of procedure-related bleeding was defined as follows: mild (endoscopic and clinical bleeding with a hemoglobin drop < 3 g and without the need for a blood transfusion), moderate (requiring a blood transfusion < 4 units and no need for an angiographic procedure), or

severe (requiring 4 or more units of blood and/or an angiographic/surgical procedure). The severity of procedure-related perforation was defined as follows: mild (uncertain or very slight leaking of contrast fluid that was medically treatable within 3 days), moderate (any defined perforation requiring 4-10 days of medical treatment), or severe (any defined perforation requiring medical treatment for >10 days and/or a surgical/percutaneous procedure).

Outcome measurements

The primary study endpoint was the success rate of biliary deep cannulation using either the T or NT technique. The secondary endpoints were incidence of adverse events (PEP, bleeding, perforation, and mortality), number of attempts at biliary cannulation, cannulation time period, and number of unintended PD cannulations.

Statistical analysis

The success rate of selective GW bile duct cannulation using a sphincterotome was 69% to 98.5%. The sample size was calculated based on the assumption of a 90% success rate for selective bile duct cannulation using the GW technique. Noninferiority was demonstrated within a margin of 10% with a 1-sided significance level of .025 and a power of 80%, with a sample size of 150 patients in each group.

Continuous data were described as mean, median, or standard deviation according to distribution, and categorical data were expressed in numerical and percentage terms. Categorical variables were compared using either the χ^2 test or the Fisher exact test, whereas quantitative variables were compared using either the Student *t* test or the Mann-Whitney U test. A *P* < .05 was considered statistically significant (for the Student *t* test and Mann-Whitney U test, *P* values were always 2-sided). PEP predictors were detected using a multivariate logistic regression model. Statistical analyses were performed using R: the R project for statistical computing, version 3.2.2 (<https://www.r-project.org>).

RESULTS

During the study period 334 patients, who met the inclusion criteria, were enrolled in this study. After randomization, 34 patients were excluded because of periampullary diverticula (*n* = 33) and ampullary neoplasm (*n* = 1). The remaining 300 patients were included and their data analyzed (150 in the T group and 150 in the NT group); demographic and clinical data are shown in Table 1. The mean age was 70 years; 50.5% were men, and the most common ERCP indication was choledocholithiasis in 252 patients (84%). The baseline characteristics were similar across the 2 study groups.

One hundred thirty-five procedures were performed by the 3 endoscopists who preferred the NT technique as

TABLE 1. Demographic and clinical data of the patients recruited in the study comparing the 2 cannulation techniques

	All patients (n = 300)	Touch group (n = 150)	No-touch group (n = 150)	P value
Gender, male	151 (50.5)	76 (51)	75 (50)	NS
Mean age, y, $\pm$ SD	70 $\pm$ 14	70 $\pm$ 15	70 $\pm$ 14	NS
Indications				
Choledocolithiasis	252 (84)	128 (85)	124 (83)	NS
Benign biliary stricture	38 (13)	19 (13)	19 (13)	NS
Cholangitis	25 (8)	13 (9)	12 (8)	NS
Biliary leak	12 (4)	6 (4)	6 (4)	NS
Intrahepatic lithiasis	5 (1.6)	3 (2)	2 (1)	NS
Sphincter of Oddi dysfunction	4 (1.5)	1 (1)	3 (2)	NS

Values are number of patients with percent in parentheses, unless otherwise noted. NS, Not significant; SD, standard deviation.

their primary cannulation approach, whereas 165 procedures were performed by the 3 endoscopists who preferred the T technique as their primary cannulation approach. The primary cannulation rate was significantly higher in the T group compared with the NT group (88% vs 54%, $P < .001$). The cannulation rate was significantly higher using the T technique compared with the NT technique also at crossover (77% vs 17%, $P < .001$).

The mean number of attempts to achieve primary CBD cannulation was 4.6 for the T group versus 5.5 for the NT group ($P = .006$). The mean cannulation time before crossover was 2.6 minutes for the T group versus 3.6 minutes for the NT group ($P < .001$), whereas mean overall cannulation time after crossover was 2.38 minutes for the T group versus 4.54 minutes for the NT group ($P < .001$).

The number of pancreatic entries with a GW was statistically higher using the T technique compared with the NT technique during the attempts at primary cannulation (.82 vs .55, $P = .037$). Also, the number of patients on whom PD GWC was carried out was statistically higher for the T group compared with the NT group (39% vs 28%, $P = .038$). After the crossover step, the mean overall cannulation success rate was similar for the 2 groups (T group 90% vs NT group 89%). When an alternative rescue cannulation technique was used, the overall successful cannulation rate was 99.3% for the T group and 98.7% for the NT group.

A rescue cannulation technique was used in 31 cases (22 needle-knife sphincterotomy, 6 double-wire cannulation, and 3 transpancreatic papillary septotomy). For 1 patient, after needle-knife sphincterotomy, cannulation failed because of prolongation of the procedure and subsequent sedation-related adverse events; the patient did not undergo further procedures and was put on observation. For 2 patients CBD cannulation failed notwithstanding the use of needle-knife precut, and the patients were treated using the percutaneous approach. Rates of overall procedure-related adverse events did not significantly differ between the 2 groups, and there was a 0 mortality

rate in both groups. Post-ERCP bleeding occurred in 6 patients, with the same rate for both groups (2%); bleeding was always mild, and all cases were managed conservatively. Perforation occurred in 2 patients, 1 in the T group and 1 in the NT group. Conservative management was successful in both cases with no need of surgery.

PEP occurred in 17 patients (5.7%; 14 mild, 1 moderate, 2 severe), and there were no significant differences in PEP rates between the 2 groups (T group 4% and NT group 7%). However, when considering the 2 groups separately, in the T group PEP occurred in 4 patients at the primary step, in 1 patient after the crossover and in 1 patient after rescue cannulation (using the double-wire cannulation technique). In the NT group, PEP occurred in 5 patients at the primary step (4 mild and 1 moderate), in 3 patients after crossover (2 mild and 1 severe), and in 3 patients after rescue cannulation (2 mild and 1 severe using the needle-knife sphincterotomy technique). During logistic regression analysis (including age, sex, PD entries or not, duration of cannulation) only the presence of PD entries emerged as a significant PEP predictor ($P < .001$) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study that compares outcomes for the use of the T and NT techniques for GW biliary cannulation. The results of this RCT confirm that GW is effective for selective biliary cannulation, with an overall cannulation rate (without rescue therapy) of 90%. These findings are consistent with the results of previous RCTs on this topic.^{16,19}

Our results revealed that the T technique is superior to the NT technique in terms of primary cannulation rates and overall cannulation rates after crossovers. These findings are in contrast with the results of previous studies in which endoscopists used the NT technique for GWC and reported a mean cannulation rate of 81% (range, 77%-83%).¹³⁻¹⁶ However, in the present study the 3

TABLE 2. Study outcomes

	All patients (n = 300)	Touch Group (n = 150)	No-touch Group (n = 150)	P value
Primary cannulation success	213 (71)	132 (88)	81 (54)	<.001
Mean no. of attempts for primary cannulation (median)	5 (4)	4.6 (4)	5.5 (5)	.006
Mean primary cannulation time, min (median)	3.11 (3)	2.6 (2)	3.6 (4)	<.001
Patients with PD entry during primary cannulation	101 (34)	59 (39)	42 (28)	.038
PD entry during primary cannulation, mean $\pm$ SD	.69 $\pm$ 1.21	.82 $\pm$ 1.29	.55 $\pm$ 1.11	.037
Patients with PD entry with successful primary cannulation	66/213 (31)	48/132 (36)	18/81 (22)	.030
PD entry in patients with successful primary cannulation, mean $\pm$ SD	.52 $\pm$.94	.64 $\pm$ 1.05	.32 $\pm$.70	.023
Patients with biliary cannulations success after crossovers	56/87 (64)	3/18 (17)	53/69 (77)	<.001
Overall cannulation success after crossovers	269 (90)	135 (90)	134 (89)	NS
Mean overall cannulation time after crossovers, min (median)	3.45 (3)	2.38 (2)	4.54 (4)	<.001
Biliary cannulations success using a rescue therapy	28/31 (90)	14/15 (93)	14/16 (88)	NS
Final biliary cannulation success	297 (99)	149 (99.3)	148 (98.7)	NS
Overall adverse events	26 (8.7)	10 (6.8)	16 (10.6)	NS
Pancreatitis	17 (5.7)	6 (4)	11 (7)	NS
Mild	14	6	8	
Moderate	1	—	1	
Severe	2	—	2	
Bleeding	6 (2)	3 (2)	3 (2)	NS
Perforation	2 (1)	1 (1)	1 (1)	NS
Others	1 (0.5)	—	1 (1)	—
Mortality	—	—	—	—

Values are number of patients with percent in parentheses, unless otherwise noted. PD, Pancreatic duct; NS, not significant; SD, standard deviation; —, none.

endoscopists who usually preferred the NT technique as a primary cannulation approach in clinical practice had a primary cannulation rate of 74%, which is comparable with the results of previous studies.

The size and morphology (small, large, and swollen) of the papilla, its orientation and relationship to the adjacent duodenum, and the direction of the intrapapillary and suprapapillary bile duct provide information as to the appropriateness of selecting the GWC approach.²⁰⁻²² Both techniques have advantages and disadvantages in respect to specific ampullary features, and the anatomic feature of the ampulla of Vater itself could be seen as a valuable means of determining which of these 2 techniques is more suitable.^{23,24} For example, a small papilla may often be smaller in size than the diameter of the tip of the standard sphincterotome; here the NT technique would be advantageous, whereas a large floppy or mobile papilla with a long intraduodenal segment would be better suited to initial sphincterotome cannulation beyond the orifice and then the intraduodenal segment straightened and the biliary cannulation subsequently done with the GW.

However, this hypothesis was considered after reviewing the cases in this present study retrospectively; the aim of this study was only to investigate the success rate

of selective bile duct cannulation and GWC adverse event rates using the T or NT techniques, so anatomic features were not included in the data set of patient characteristics in the study protocol. Therefore, we suggest that further studies are needed to confirm this hypothesis to evaluate the potential role of each cannulation technique for specific anatomic features. Furthermore, in cases of confined duodenal space, which allows only limited movement of the duodenoscope, the NT technique fails because of the inability to obtain the ideal angle of the sphincterotome in regard to the axis of CBD. In this situation, cannulation can be achieved only by touching the papilla.

Another reason for carrying out this study was that we believed it possible that the use of the NT technique may cause less mechanical trauma because of less manipulation of the sphincterotome across the ampulla as mechanical trauma has been associated with ERCP adverse events, especially PEP.^{7,8} The results of this RCT confirmed that GW is also safe for biliary cannulation, with an overall adverse event rate of 8.7% and a PEP rate of 5.7%. In addition, our results show that the overall procedure-related adverse event rates and PEP did not significantly differ between the 2 groups, even when considering the 3 steps (primary cannulation, crossover, and rescue cannulation) for each group.

When logistic regression analysis was done, only the presence of PD entries emerged as a significant PEP predictor. Even though our belief that the NT technique could minimize ampullary damage appeared to be confirmed, this approach resulted in an increased numbers of cannulation attempts and an increased amount of time for CBD cannulation. However, although overall average PD entries was higher for the T group, when the patients who developed PEP were taken into consideration, the average number of unintended PD entries did not differ between the 2 groups. An important limitation of this study is that patients with malignant strictures were not included. This was a deliberate choice because pancreatic cancer patients are somewhat protected from the development of PEP as their bodies become accustomed to obstruction of the PD and the hilar malignant stricture location is particularly prone to the development of cholangitis.²⁵⁻²⁷

In conclusion, our study suggests that if benign biliary indications are present, the T technique is superior for biliary cannulation compared with the NT technique, in terms of cannulation success rate, number of attempts, and time for cannulation. Although the number of pancreatic entries with a GW was statistically higher using the T technique compared with the NT technique, the PEP rate was slightly higher for the NT technique; it is possible that the cannulation time and the number of attempts are important contributing factors. It is also important to note that endoscopists should be skilled in the use of both techniques because the choice of which technique is most suitable is directly related to the anatomy of the papilla and duodenum, and which technique is chosen should not be determined only by the normal technique preference of the endoscopist.

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