Rectal Indomethacin Does not Prevent Post-ERCP Pancreatitis in Consecutive Patients

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Abstract

Background & Aims—Rectal indomethacin, a non-steroidal anti-inflammatory drug, is given to prevent pancreatitis in high-risk patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), based on findings from clinical trials. European Society for Gastrointestinal Endoscopy guidelines recently recommended prophylactic rectal indomethacin for all patients undergoing ERCP, including those at average risk for pancreatitis. We performed a randomized controlled trail to investigate the efficacy of this approach.

Methods—We performed a prospective, double-blind, placebo-controlled trial of 449 consecutive patients undergoing ERCP at Dartmouth Hitchcock Medical Center, from March 2013 through December 2014. Approximately 70% of the cohort were at average-risk for PEP. Subjects were randomly assigned to groups given either a single 100 mg dose of rectal indomethacin (n=223) or a placebo suppository (n=226) during the procedure. The primary outcome was the development of post-ERCP pancreatitis (PEP), defined by new upper-abdominal pain, a level of lipase greater than 3-fold the upper limit of normal, and hospitalization following ERCP for 2 consecutive nights.

Results—There were no differences between the groups in baseline clinical or procedural characteristics. Sixteen patients in the indomethacin group (7.2%) and 11 in the placebo group (4.9%) developed PEP (*P*=.33). Complications and the severity of PEP were similar between groups. Per a priori protocol guidelines, the study was stopped due to futility.

Conclusions—In a randomized controlled study of consecutive patients undergoing ERCP, rectal indomethacin did not prevent post-ERCP pancreatitis. ClincialTrials.gov no: NCT01774604

Keywords

pancreas; NSAID; inflammation; ESGE recommendation

Introduction

Acute pancreatitis (AP) is the most common gastrointestinal indication for admission to the hospital in the United States.[1] Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most prevalent iatrogenic cause, leading to substantial morbidity, occasional mortality, and a significant economic impact to the United States healthcare system.[2,3] Due to the clinical and economic burden of PEP, extensive research efforts have been devoted to its prevention.[4-5] Among the most promising interventions to prevent PEP is the use of periprocedural rectal non-steroidal anti-inflammatory drugs (NSAIDs).[6-7]

Rectal NSAIDs are thought to regulate pro-inflammatory mediators in AP by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet-activating factors.[6,8] One NSAID in particular, rectal indomethacin, has been used extensively since 2012 following the publication of a randomized, placebo-controlled trial in patients undergoing ERCP considered to be at high risk for PEP.[8] The trial found that a single 100 mg dose of rectal indomethacin significantly reduced the risk of PEP from 16.9% in those receiving placebo to 9.2% in those receiving indomethacin. As a result of this study and others, the European Society for Gastrointestinal Endoscopy (ESGE) in 2014 recommended routine rectal administration of 100 mg indomethacin or diclofenac during ERCP in *all* patients without contraindication.[9] However, despite these recommendations, the use of rectal NSAIDs in patients not considered to be at high-risk for PEP (the "average-risk" patient) is unproven.

In order to determine the benefit of rectal indomethacin in preventing PEP in all patients, we conducted a prospective, randomized, double-blind, placebo-controlled trial in consecutive patients undergoing ERCP.

Methods

Study Design

We enrolled patients at a single, tertiary care, academic medical center in the United States after approval from the Committee for the Protection of Human Subjects (IRB) at Dartmouth-Hitchcock Medical Center (CPHS#23749). An independent data and safety monitoring board provided regulatory oversight by reviewing blinded subject data, analyzing complications, and performing scheduled in-term analysis. The study was designed under the auspices of the CONSORT guidelines.[10]

Patients

The inclusion criteria were defined as consecutive patients undergoing ERCP (+/- endoscopic ultrasound [EUS]) at Dartmouth-Hitchcock Medical Center in Lebanon, NH. All patients were adults greater than 18 years-old who were able to provide written, informed consent. Consent was obtained by the therapeutic endoscopist or interventional fellow at the time of informed consent for the procedure. Exclusion criteria included all patients with active acute pancreatitis, those in whom ERCP was performed for diagnosis and/or treatment of acute pancreatitis, contraindication to NSAID therapy (serum creatinine >1.4 mg/dL or active peptic ulcer disease), previously documented allergy to NSAIDs, pregnant or nursing mothers, inability to provide written informed consent, those who had been previously randomized within the last 30 days, those <18 years of age, or those without a rectum (i.e. status post total proctocolectomy). Eligible patients who provided written informed consent and met inclusion criteria were randomized after the major papilla was reached and attempts at cannulation initiated (Figure 1). Randomization was performed in a block format prior to study initiation by the Dartmouth Investigational Pharmacy with the investigators blinded to treatment allocation. Pre-made envelopes with allocation and study number ensured randomization concealment until interventions were assigned.

Intervention

All procedure-related maneuvers and interventions were managed by two experienced therapeutic endoscopists. Following attempted cannulation, two 50 mg indomethacin suppositories (Cardinal Health, Dublin, OH) or two inert placebo suppositories (Letco Medical, Decatur, AL) were administered by the nurse in the procedure room if the patient had met all inclusion criteria and signed written, informed consent. The suppository was given per rectum during the ERCP. The endoscopist and patient were blinded to the study allocation.

The number of cannulation attempts, the use and type of pancreatic duct stents, the use of wire-guided cannulation, the amount of periprocedural intravenous fluid, and the participation of an advanced endoscopy fellow were factors all at the discretion of the treating endoscopist and were not specifically outlined in the study protocol.

Outcomes

The primary study outcome was whether 100 mg of rectal indomethacin compared to placebo would lower the rate of PEP in all patients undergoing ERCP. The secondary outcome was to assess the severity of PEP in those receiving indomethacin versus placebo. PEP was defined if the following three conditions were met – new onset upper abdominal pain, an elevated lipase greater than three times the upper limit of normal 24 hours after the onset of pain, and hospitalization for at least two nights. Severity of pancreatitis was defined per the Revised Atlanta Classification.[11]

Following ERCP, patients were observed in the recovery area per institutional guidelines for at least ninety minutes. If there was new pain requiring admission, the patient was admitted to the hospitalist medicine service. Subsequent care was left to the discretion of the inpatient

service team and supporting gastrointestinal consult service, both of whom were unaware of study-group assignments.

All patients were contacted by telephone five days following the ERCP to determine whether they developed PEP. All patients were then again contacted thirty days after the procedure to assess for delayed complications and/or PEP. ERCP procedural elements, patient demographics, and follow-up data were recorded on standardized data-collection forms by the primary investigator who was unaware of the patient/study-group assignments. All co-authors had access to the study data, reviewed, and approved the final manuscript.

Adverse Events

All complications of the procedure, adverse events that were potentially attributed to the study drugs, and any death from any cause within 30 days of enrollment were reported to the local institutional review board (IRB) as well as the data and safety monitoring board. The IRB requested not to report PEP as it is an expected event following ERCP.

Statistical Analysis

We estimated that 1,398 patients (699 per study group) would provide a power of 80% to detect a 50% reduction in the rate of PEP from 5% in the placebo group to 2.5% in the indomethacin group using the two-tailed Fisher's Exact test with a two-sided significance of 0.05.[12] The prevalence of PEP was based on internal estimates of the past rate of PEP in patients undergoing ERCP at our medical center.

Continuous variables were evaluated using the student's t-test and categorical variables using the Fisher's Exact test. Exploratory subgroup analysis by calculating relative risks was performed for pre-specified factors which conveyed a higher risk for PEP - pancreatic stent placement, suspected sphincter of Oddi dysfunction, history of PEP, difficult cannulation, wire cannulation of the pancreatic duct, pancreatography, pancreatic acinarization, therapeutic biliary sphincterotomy, therapeutic pancreatic sphincterotomy, balloon dilation of the biliary sphincter, and trainee involvement in the ERCP.[13]

Scheduled interim analysis was to be performed after 350 patients were enrolled (25% of predicted enrollment) to ensure safety and assess the primary outcome. *A priori* stopping guidelines were instituted including a p-value of <0.020 showing benefit of indomethacin versus placebo, or evidence of futility to reach a statistical different outcome between the study groups.

Results

Patients

From March 2013 to December 2014, all patients undergoing ERCP at our institution were screened for eligibility and offered inclusion into the study if eligible (See Figure 1). 449 patients were eventually enrolled into the study. In May 2014, the data and safety monitoring committee evaluated the first 350 patients and due to indomethacin's lack of efficacy, recommended continued enrollment with 75 more patients randomized. In December 2014, the board recommended termination of the study due to futility of the

anticipated primary end point after reviewing these additional 75 patients. Due to the lag time between enrollment and 30 day study follow-up requirements, an additional 24 patients were enrolled and are included in the study analysis. Thus, a total of 223 patients received indomethacin and 226 received placebo. Follow-up of all patients for primary and secondary end-points was completed.

Baseline characteristics were similar in both groups (See Table 1). Only 14 patients (2.8%) had suspected sphincter of Oddi dysfunction and 37 (7.4%) had planned interventions to their pancreatic duct due to a pancreatic duct stricture, disruption, or stone. Table 2 demonstrates the procedural characteristics. There was no difference in the rates of sphincter manipulation, biliary and/or pancreatic duct stenting, or previous biliary and/or pancreatic sphincterotomy.

Study Outcomes

The primary outcome of PEP occurred in 27 of 449 patients (6.0%) - 16 of 223 (7.2%) occurred in the indomethacin group and 11 of 226 (4.9%) occurred in the placebo group (p=0.33) (Figure 2). All 27 patients with PEP completed 30 days of follow-up (or until time of death) to assess the severity of pancreatitis. Severe or moderately severe PEP occurred in 0 of 223 receiving indomethacin while 1 of 226 (0.4%) had severe PEP (p=1.0) and 1 of 226 had moderately severe PEP receiving placebo (0.4%) (p=1.0). The patient with severe PEP in the placebo group died secondary to untreated acute renal failure following diagnostic and palliative EUS/FNA and ERCP with biliary stenting for metastatic pancreatic cancer, opting for comfort care only. The two other deaths in the placebo group were not secondary to pancreatitis: one with known multifocal hepatocellular carcinoma died from secondary bacterial peritonitis in the setting of decompensated ascites and one from a witnessed aspiration event in the hospital two days post-procedure. No necrotizing pancreatitis occurred in either group. There was no difference in rates of gastrointestinal bleeding, death, or 30 day hospital readmission (p= 0.75, 0.25, and 0.10 respectively) (Figure 2).

Exploratory subgroup analysis

Table 3 demonstrates that there was no one-directional trend toward benefit in terms of relative risk reduction for indomethacin vs. placebo. Of note, there was an increased rate of pancreatitis in those who underwent dual therapy of rectal indomethacin and pancreatic duct stenting, although this did not meet statistical significance (8 of 16 patients in the indomethacin group and 4 of 11 in the placebo group with a relative risk reduction of -28%).

In patients with biliary manipulation only, 3 of 124 (2.4%) in the placebo group and 2 of 125 (1.6%) in the indomethacin group had PEP (p=0.68). In patients with pancreatic ductal instrumentation only, 3 of 28 (10.7%) in the placebo group and 6 of 32 (18.8%) in the indomethacin group developed PEP (p=0.48). Manipulation of both ducts (including wire access only) resulted in PEP in 5 of 70 (7.1%) patients in the placebo group and 8 of 70 (11.4%) in the indomethacin group (p=0.79).

Discussion

Our findings demonstrate that giving a single 100 mg of rectal indomethacin in consecutive individuals undergoing ERCP does not prevent PEP. These results are in contrast to recent studies highlighting the benefit of rectal NSAIDS to prevent PEP in high-risk patients.[8] In addition, our results counter the guidelines espoused by the European Society for Gastrointestinal Endoscopy, which recently recommended giving rectal indomethacin to prevent PEP in *all* patients undergoing ERCP.[9]

This study did not exclude patients based on indication or intervention; it was deliberately designed to mirror the unenhanced patient population that is encountered most frequently in general gastroenterology practice. It also did not pre-determine the interventions of the treating endoscopist for each patient; again this was by design in order to most directly mirror typical clinical practice. Fortunately, randomization was successful in terms of both baseline patient characteristics and procedural interventions. In addition, the study deliberately did not categorize patients into high and low-risk for PEP to maintain appropriate randomization and there was no evidence of increased PEP in high-risk patients, nor benefit of rectal indomethacin in this group. A potential study limitation, however, is that patients were enrolled at a single center.

The overall rate of PEP (6%) was consistent with our pre-study estimates, which is much lower than the mean rate of PEP in previous studies of high-risk patients in NSAID pharmacoprevention studies.[8] This finding supports the characterization of this study population as unenhanced toward a high-risk group and suggests that the conclusions reached in prior studies are not generalizable to all patients undergoing ERCP.

There is a clear benefit of using rectal NSAIDs to prevent PEP in high-risk individuals as demonstrated in the study by Elmunzer *et al.*[8] Since this manuscript was published, many institutions have begun using rectal indomethacin in all patients undergoing ERCP.[14] However, our findings suggest that universal prophylaxis using rectal indomethacin for PEP is not beneficial and should not be recommended.

The ESGE guidelines are based on meta-analyses of several small studies and then larger studies in high-risk patients.[15-22] Currently, there are no major American endoscopy society guidelines that specifically recommend using rectal NSAIDs to prevent PEP in all patients.[23] One might argue that since rectal NSAIDs are inexpensive with little chance of causing clinically relevant side effects, the benefit of occasionally preventing PEP outweighs the minimal risk. However, guidelines that promulgate universal prophylaxis based on presumptive application to groups not fully studied are not justified and should not be endorsed. Not only can assumptions lead to unnecessary medication usage and charges, they can also lead to unsubstantiated medico-legal liability.

The role of pancreatic duct stenting in combination with rectal NSAIDs has yet to be determined.[24-5] In this study, there was an increased rate of pancreatitis in those who had the dual therapy of rectal indomethacin and pancreatic duct stenting. Further investigation is needed to evaluate the role of rectal NSAID therapy to prevent PEP in the context of pancreatic duct stenting. Until definitive comparative effectiveness trials are performed,

pancreatic duct stenting has been, and should remain, a critical component of reducing PEP and in our opinion should be employed whenever wire access to the pancreatic duct and/or pancreatography is performed.

There was no protective benefit found with previous sphincterotomy in this study, which mirrors similar results in other large studies evaluating risk factors for PEP. For example, in a large prospective multi-center cohort study, previous sphincterotomy had a non-significant increased risk of PEP compared to those with a native papilla (7.8 vs 6.2%, p=0.22).[26] Furthermore, prior sphincterotomy was only one of nine of the 32 variables in that study which did not reach significance in univariate or multivariate analysis as protective against PEP.

In summary, prophylactic rectal indomethacin did not reduce the incidence or severity of PEP in consecutive patients undergoing ERCP. Guidelines that recommend the administration of rectal indomethacin in all patients undergoing ERCP should be reconsidered.

Acknowledgments

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Abbreviations

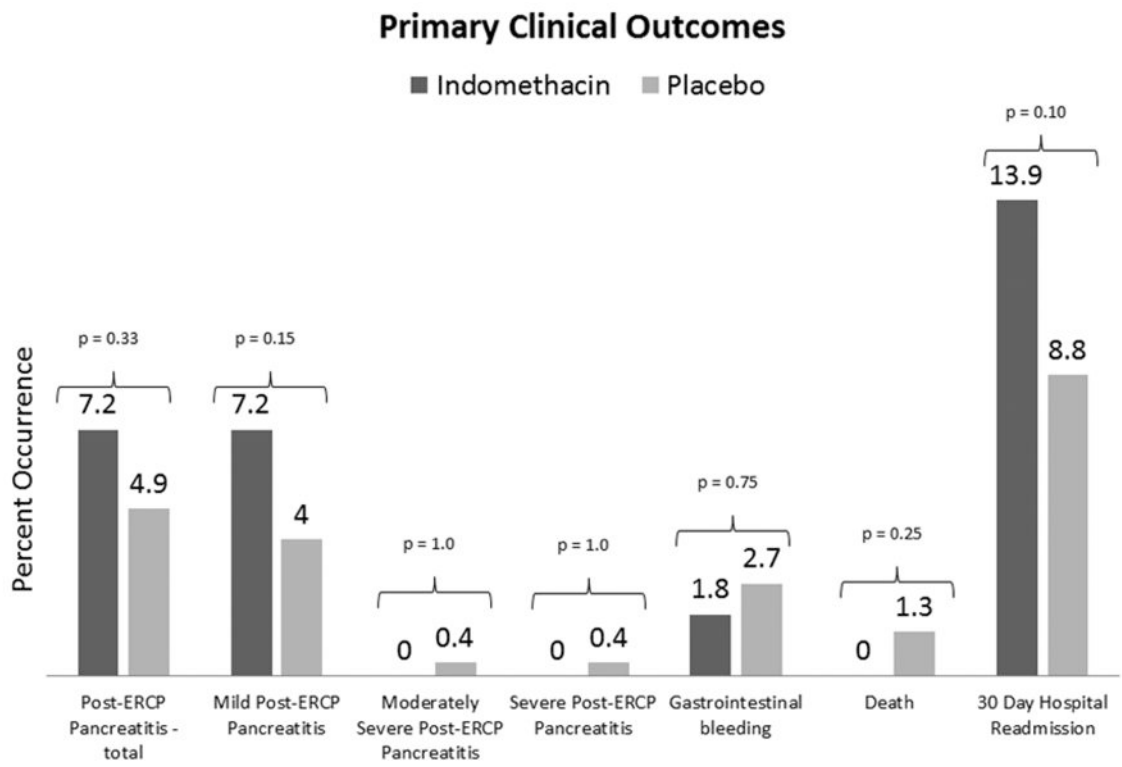|	
endoscopic retrograde cholangiopancreatography (ERCP)	endoscopic ultrasound (EUS), fine needle aspiration (FNA), nonsteroidal anti-inflammatory drugs (NSAID), post-ERCP pancreatitis (PEP)
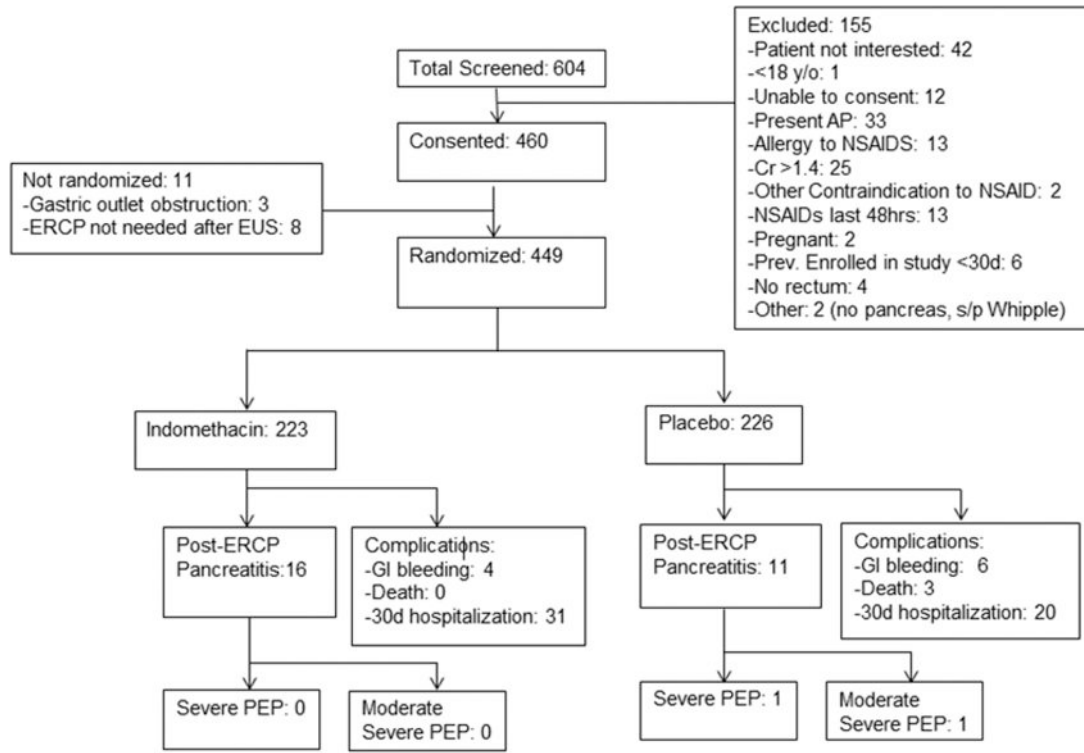
Figure 1. Enrollment and Outcomes

Figure 2. Primary Clinical Outcomes

Table 1

Baseline Patient Characteristics

Characteristic	Indomethacin (n=223)	Placebo (n=226)	P value
Age – yr	64.9	64.3	0.68
Female Sex – no. (%)	118 (52.9)	118 (52.2)	0.92
Indication – no. (%)			
Acute Cholangitis	12 (5.4)	13 (5.8)	1.00
Choledocholithiasis	59 (26.4)	52 (23.0)	0.44
Malignant Biliary Obstruction[*]	53 (23.8)	50 (22.1)	0.74
Biliary Stent Change	25 (11.2)	25 (11.1)	1.00
Biliary Leak	11 (4.9)	12 (5.3)	1.00
Elevated Liver Tests/Jaundice	13 (5.8)	9 (4.0)	0.39
Pancreatic Stricture	3 (1.3)	5 (2.2)	0.72
Suspected Sphincter of Oddi Dysfunction	6 (2.7)	8 (3.5)	0.79
Pancreatic Leak/Disruption	11 (4.9)	12 (5.3)	1.00
Pancreatic Duct Stone	3 (1.3)	2 (0.9)	0.68
Recurrent Acute Pancreatitis	5 (2.2)	2 (0.9)	0.28
Ampullectomy	6 (2.7)	5 (2.2)	0.77
Other[†]	16 (7.2)	31 (13.7)	**0.03**
History of post-ERCP pancreatitis – no. (%)	9 (4.0)	9 (4.0)	1.00
Previous Sphincterotomy – no. (%)	72 (31.8)	71 (31.4)	0.61
Previous ERCP – no. (%)	81 (36.3)	79 (35.0)	0.77

[*] Malignant biliary obstruction includes pancreatic head malignancy, cholangiocarcinoma and indeterminate biliary stricture

[†] Most common indications for "other" included primary sclerosing cholangitis, papillary stenosis, and choledochal cyst evaluation

Table 2

Procedural Characteristics

Characteristic	Indomethacin (n=223)	Placebo (n=226)	P value
Sphincter Manipulation			
Difficult Cannulation (>8 attempts) – no. (%)	46 (20.6)	42 (18.4)	0.64
Precut Biliary Sphincterotomy	11 (4.9)	16 (7.0)	0.43
Therapeutic Biliary Sphincterotomy – no. (%)	106 (46.9)	114 (50.9)	0.57
Therapeutic Pancreatic Sphincterotomy – no. (%)	12 (5.4)	5 (2.2)	0.08
Minor Duct Sphincterotomy – no. (%)	5 (2.2)	4 (1.8)	0.75
Balloon Dilation of Biliary Sphincter – no. (%)	21 (9.4)	20 (8.8)	0.87
Pancreatic Duct Manipulation			
Wire Cannulation of Pancreatic Duct – no. (%)	90 (40.3)	89 (31.4)	0.85
Pancreatography – no. (%)	50 (22.4)	49 (21.7)	0.97
Pancreatic Acinarization – no. (%)	5 (2.2)	4 (1.8)	0.75
Stent Placement			
Biliary Stent Placement – no. (%)	89 (39.9)	84 (37.2)	0.56
Pancreatic Stent Placement – no. (%)	36 (16.1)	35 (15.5)	0.90
Other Interventions			
Trainee Involvement in ERCP – no. (%)	152 (68.2)	168 (74.3)	0.18
Concomittant EUS/FNA – no. (%)	41 (18.4)	40 (17.7)	0.90
Periprocedural Fluid Volume - ml	705	703	0.95

Table 3

Exploratory SubGroup Analysis of Patients with Post-ERCP Pancreatitis

	Patients with PEP		% Relative Risk Reduction (Indomethacin vs. Placebo)
	Indomethacin (n=16)	Placebo (n=11)	
Pancreatic Stent Placement – no. (%)	8 (50)	4 (36)	-28%
Suspected Sphincter of Oddi Dysfunction – no. (%)	1 (6)	1 (9)	+33%
History of Post-ERCP Pancreatitis	2 (13)	1 (9)	-21%
Difficult Cannulation	6 (38)	5 (45)	+16%
Wire Cannulation of Pancreatic Duct – no. (%)	13 (81)	7 (64)	-21%
Pancreatography – no. (%)	8 (50)	8 (73)	+32%
Pancreatic Acinarization – no. (%)	2 (13)	0 (0)	NA
Therapeutic Biliary Sphincterotomy – no. (%)	7 (44)	3 (27)	-39%
Therapeutic Pancreatic Sphincterotomy – no. (%)	2 (13)	3 (27)	+52%
Balloon Dilation of Biliary Sphincter – no. (%)	0 (0)	1 (9)	NA
Trainee Involvement in ERCP – no. (%)	12 (75)	8 (73)	-3%