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"Efficacy of combined rectal indomethacin and sublingual nitroglycerin before ERCP in reducing the risk of post-ERCP pancreatitis"

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Abstract
Introduction: *The use of endoscopic retrograde cholangiopancreatography (ERCP), as a treatment for benign and malignant pancreaticobiliary tree disorders is becoming widely accepted. Pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP), accounting for substantial morbidity, and mortality. Most recently, interest has been developed in the study of non-steroidal anti-inflammatory drugs (NSAIDs) to prevent PEP. This study aimed to evaluate the efficacy of combined rectal indomethacin and sublingual nitroglycerin before ERCP in reducing the risk of post-ERCP pancreatitis.*
Methods: *This was a randomized controlled trial conducted in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from July, 2019 to September, 2020. In our study, we included 50 hospitalized patients who were >18 years old undergoing ERCP based on clinical indication and proper investigation.*
Result: *We found the mean age was 50.78 ± 14.24 years. Most of our patients were female (56%) compared to male (44%). The most common indication of ERCP was choledocholithiasis (36%). There was no significant difference between the mean value of serum amylase and serum lipase before ERCP. Median values 2hrs and 24hrs after ERCP have no significant difference either. We found only 2 (4%) moderate PEP after ERCP. The most common symptom after ERCP was abdominal pain and the most common side effect was a fall in systolic blood pressure.*
Conclusion: *Our study demonstrated that using sublingual GTN in conjunction with indomethacin suppositories prevents post-ERCP pancreatitis. A trend toward less severe pancreatitis was observed in the combination therapy.*
Keywords: *Efficacy, Rectal indomethacin, Sublingual nitroglycerin, ERCP*

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I. Introduction

The use of endoscopic retrograde cholangiopancreatography (ERCP), as a treatment for benign and malignant pancreaticobiliary tree disorders is becoming widely accepted. However, because it's an invasive operation, there are significant risks for the patient.[1] Acute pancreatitis is the most common and dreaded side effect of ERCP, with a high risk of morbidity and possibly even mortality. [2] Tenner and Steinberg (2016)

showed that 35–70% of post-ERCP cases had asymptomatic hyperamylasemia. A history of therapeutic ERCPs (7%), diagnostic ERCPs (5%), and clinical acute pancreatitis (25%) are all linked to a history of post-ERCP pancreatitis (PEP). [3]

Pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP), accounting for substantial morbidity, occasional mortality, and increased healthcare expenditures.[4] Prostaglandins and neutrophil-mediated endothelial injury are all believed to play an important role in the pathogenesis of acute pancreatitis which is why most recently, interest has been developed in the study of non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of PEP. NSAIDs are potent inhibitors of phospholipase A2. [5,6]

Nitrates also have a role in the prevention of post-ERCP pancreatitis. Systemically administered GTN may relax the human sphincter of Oddi, facilitating the extraction of common bile duct stones without endoscopic sphincterotomy. In addition by relaxing the sphincter of Oddi, GTN potentially corrects one possible mechanism of post-ERCP pancreatitis i.e. pancreatic duct obstruction due to sphincter spasm.[7]

Sudhindran et al. suggested that sublingual GTN (2 mg) before ERCP could relax sphincters, induce intubation, and reduce 10% postoperative pancreatitis.[8] Two small series reported that sublingual GTN (0.6–3.6 mg) facilitated the extraction of CBD stones (diameter 6-12 mm) without the need for endoscopic sphincterotomy. [9,10]

Bai et al. in their meta-analysis of randomized, double-blind, placebo-controlled trials found that the incidence of PEP in the GTN group and placebo group was 5.9% and 9.8%, respectively. Also, patients who received GTN had a 39% less chance of developing PEP.[11] Meta-analysis showed that the prophylactic use of GTN is an effective and relatively safe intervention for preventing PEP and hyperamylasemia.[12]

As a measure of preventing PEP Sotoudehmanesh, et al. conducted a randomized trial with a combination of sublingual nitrates and indomethacin vs indomethacin alone where they suggested that the aforementioned combination of drugs is more effective in reducing PEP incidence than indomethacin by itself.[13] Rectal NSAIDs (diclofenac sodium and indomethacin) are the preferred method for reducing the incidence of PEP. Due to their good safety profile, low price, and easy availability, at this moment NSAIDs are the best pharmacological prophylactic method.[14] As a result, routine rectal administration of 100 mg of indomethacin, immediately before or after ERCP, is recommended (recommendation grade A) in the guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE).[15]

Several studies have been conducted to assess the individual efficacy of NSAIDs and nitrates to establish their role in preventing post-ERCP pancreatitis. However, the combined effect of NSAIDs and nitrate to prevent post-ERCP pancreatitis is not known though their mechanism of action in preventing PEP is different and there is no drug interaction between them. Therefore, this study aimed to evaluate the efficacy of combined rectal indomethacin and sublingual nitroglycerin before ERCP in reducing the risk of post-ERCP pancreatitis.

II. Methodology & Materials

This was a randomized controlled trial conducted in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from July, 2019 to September, 2020. In our study, we included 50 hospitalized patients who were >18 years old undergoing ERCP based on clinical indication and proper investigation.

Inclusion criteria:
a) Patients undergoing ERCP based on clinical indication and proper investigation
b) Patients aged >18 years of both sexes.

Exclusion criteria:
a) Patients with recent (within 4 weeks) gastrointestinal (GI) hemorrhage; b) Patients with Coagulopathy or received anticoagulant within 3 days before ERCP; c) Patients with previous sphincterotomy; d) Patients with known allergy/hypersensitivity to NSAIDs and nitrates; e) Patients with chronic calcific pancreatitis, ampullary tumor, and pancreatic malignancy; f) Patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD etc.) were excluded from our study.

Study procedure: Our study patients were given an indomethacin suppository (Indomet100 mg) plus sublingual glyceryl trinitrate (Anril spray 5 puff) 5 minutes before ERCP. The ERCP procedures were performed with the patient after administration of sedation (propofol and fentanyl) intravenously, with dosage at the discretion of the endoscopist. Patients received complementary oxygen (3 to 5 l/min) through a nasal cannula and infusion of 500 ml to 1000 ml of 0.9 % normal saline. The material used to perform ERCP consisted of a video duodenoscope model TJF-150 (Olympus™), conventional wire sphincterotome for selective cannulation of the bile duct, needle knife to perform the precut sphincterotomy, hydrophilic guide wire via catheter through the bile duct cholangiogram or stenting, Dormia basket and/or stone extraction balloon or trapezoid lithotripsy

basket for stone extraction, plastic biliary stents and self-expandable metal stents (SEMS) for drainage and dilation of benign and malignant biliary stricture and nonionic water-soluble contrast Inj. Iopamiro in concentration of 370 mg/ml (BRACCO™ 370) for opacification of the biliary and pancreatic ducts. All accessories that were used for ERCP from Olympus™ or Boston Scientific. All patients were monitored continuously during the procedure, with measurements of blood pressure, heart rate, respiratory rate and arterial oxygen saturation.

Follow-up: Patients were kept under surveillance in the endoscopy recovery area for 3 hours after ERCP. Measurement of serum amylase and lipase was performed 3 times: before ERCP, 2 hours, and 24 hours after ERCP. Patients who developed abdominal pain during this observation period were generally kept in the hospital to exclude procedural complications, including pancreatitis and perforation. The decision to prolong hospitalization was left to the discretion of the endoscopist and clinical service, respectively. Patients who developed PEP were also observed to evaluate PEP-related or unrelated complications.

Data Analysis: All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. The differences between groups were analyzed by unpaired t-test, chi-square (X^2) test, fisher's exact test, Mann-Whitney U test, etc. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 23 (Statistical Package for Social Sciences) for Windows version 10. The study was approved by the Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University.

III. Results

A total of 50 patients who underwent ERCP and fulfilled the selection criteria, were included in this study. The result of the study is presented in the following tables.

Table 1: Age distribution of the study subjects (N=50)

Demographic profile	N	P(%)	P-value
Age (years)			
≤30	7	14	
31 – 40	3	6	
41 – 50	14	28	
51 – 60	17	34	
>60	9	18	
Mean ± SD	50.78 ± 14.24		0.455

Figure 1: Gender distribution of our study patients

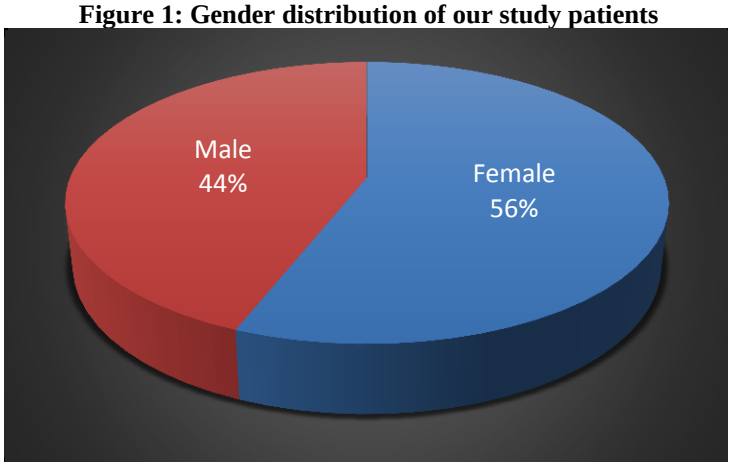

Table 2: Indications of ERCP and Biochemical parameters of the study subjects

Indication of ERCP	N	P(%)	P-value
Choledocholithiasis	18	36.0	
Cholangiocarcinoma	13	26.0	
Benign Biliary stricture	8	16.0	
Carcinoma GB infiltrating biliary tree	9	18.0	
Recurrent pyogenic cholangitis	2	4.	
Biochemical parameters			
Serum creatinine (mg/dl)	0.92 ± 0.54		0.004
Serum calcium (mg/dl)	9.88 ± 0.69		0.003
Serum Albumin (g/L)	39.82 ± 6.49		<0.001
Serum Bilirubin (mg/dl)	8.27 ± 7.57		0.001
Alkaline phosphatase (IU/L)	388.48 ± 245.70		0.011

Random blood sugar (mmol/L)	7.69 ± 4.21	0.044
C-reactive protein (CRP)	2.58 ± 2.24	0.366

Table 3: Serum amylase before and after ERCP (N=100)

Sample collection time	(Mean ± SD)	P-value
Serum amylase level (IU/L)		
Before ERCP	38.90 ± 7.75	0.591
2 hours after ERCP	64.46 ± 20.07	0.256
24 hours after ERCP	64.00 ± 17.48	0.294
Serum lipase level (IU/L)		
Before ERCP	46.92 ± 10.96	0.311
2 hours after ERCP	62.98 ± 20.09	0.600
24 hours after ERCP	58.06 ± 14.63	0.222

Table 4: Post-ERCP pancreatitis and Severity of pancreatitis (N=100)

Pancreatitis	N	P(%)	p-value
Present	2	4.0	0.02
Absent	48	96.0	
Severity of pancreatitis			
Mild	0	0	0.23
Moderate	2	4.0	
Severe	0	0	

Table 5: Common gastrointestinal symptoms and drug-induced adverse effects (*n*=100).

Symptoms	N	P(%)	P Value
Abdominal pain after ERCP	5	10.0	0.062
Radiation of pain in the back	2	4.0	0.240
Nausea/vomiting	1	2.0	0.001
Adverse effects			
Fall of SBP	3	6.0	0.242
Dizziness	2	4.0	1.00
Headache	1	2.0	0.617

IV. Discussion

In this study mean age of the study population was 50.78+14.24 years. Sotoudehmanesh et al. and Sarkeshikian et al. found the mean ages 58.40+17.8 and 60.64 + 19.31 years respectively. This age variation may be due to the short life expectancy in our country. [13,16]

Most of our patients were female (56%) compared to male (44%). Sarkeshikian et al. and Hajalikhani et al. found slight female preponderance in each group which is consistent with this study. [16,17] Tomoda et al. found male preponderance in each group which is not consistent with this study. [18]

The most frequent indication of ERCP was choledocholithiasis, observed in 18 cases (36.0 %) of our study patients. Sotoudehmanesh et al., Tomoda et al, and Sarkeshikian et al. also found that choledocholithiasis is the most common diagnosis followed by malignant biliary obstruction. [13,16,18]

This study showed that PEP after ERCP was found in 2 (4%) patients with a significant p-value. There were only 2 cases of moderate PEP. Cotton & Yaghoobi found most of their cases were mild (<3 days in hospital), about 20% moderate (3-10 days), 5% severe, and 1% fatal. [19]

In this study, pre-ERCP amylase level was 38.90 ± 7.75, (p=0.591). Montano Loza, et al. showed 53.56 ± 22 IU/L, (p = 0.38), which is consistent with this study.[20] In this study, median serum amylase level 2 hours after ERCP, was 64.46 ± 20.07 IU/L. After 24 hours median serum amylase was 64.00 ± 17.48 IU/L. A study done by Tenner and Steinbergh found serum amylase values above 276 IU/L (normal 30 to 70 IU/L) and lipase above 1000 IU/L (normal 45 to 110 IU/L) 2 hours after completing the procedure had almost a 100% positive predictive value for post-ERCP pancreatitis.[3]

PEP developed in 4% of our patients which is consistent with the study of Sotoudehmanesh et al. who found 6.7% and Tomoda et al. found 5.6% in their study. [13,18] Another study by Sarkeshikian et al. found it 5.1%. [16] Mild adverse effects concerning the use of nitrate, including dizziness, headache, or transient fall of SBP were detected in this study. Tomoda et al. found no serious adverse event related to the additional administration of sublingual nitrate and Moreto et al found the same adverse effects as us.[18,21]

In this study, the combination of NSAIDs and nitrate was found effective in preventing post-ERCP pancreatitis.

V. Limitations

This was a single-center study with small sample size due to short study period. The study was done during the COVID-19 pandemic, so there was lack of availability of the patients. After evaluating those patients, long term follow-up with them was not possible.

VI. Conclusion

This study observed the efficacy of the combination of indomethacin suppository and sublingual GTN. It was demonstrated that the use of sublingual GTN in conjunction with indomethacin suppositories prevents post-ERCP pancreatitis. A trend toward less severe pancreatitis was observed in the combination therapy group, even though there was no statistically significant difference in pancreatitis severity.

VII. Recommendations

A further study with a prospective and longitudinal study design including a larger sample size needs to be done to establish the efficacy of combined rectal indomethacin and sublingual GTN in preventing post-ERCP pancreatitis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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