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## Case Series

# Epinephrine in the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Preliminary Study

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## Keywords

Endoscopic retrograde cholangiopancreatography · Post-endoscopic retrograde cholangiopancreatography pancreatitis

## Abstract

**Background:** Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ERCP pancreatitis (PEP) ranges between 15 and 20% among patients at high risk of developing PEP. The efficacy of indomethacin administration in the prevention of PEP is rather debatable. In the present randomized trial study, we evaluated whether or not the combination of indomethacin and epinephrine in comparison to the single administration of indomethacin differs in the pathogenesis

and prevention of post-ERCP pancreatitis. **Patients and Methods:** One hundred and ninety-two patients were randomized in a double-blinded manner into 3 groups: the epinephrine group (group A), the indomethacin group (group B), and the combined epinephrine and indomethacin group (group C). After the procedure, patients were evaluated for the PEP development. **Results:** During the procedure, 66 patients were randomized to the epinephrine group (group A), 68 cases to the indomethacin group (group B), and 58 individuals to the indomethacin-epinephrine group (group C). The mean age of patients in the epinephrine group was  $59.59 \pm 15.680$  years, in the indomethacin group it was  $58.06 \pm 17.125$  years, and in the combination group it was  $59.62 \pm 15.369$  years. In the present study, we did not observe a significant difference between the 3 groups in sex, age, pre-ERCP amylase, lipase, and patient and procedure risk factors including pancreatic duct (PD) dilation ( $p = 0.404$ ), PD cannulation ( $p = 0.329$ ), and difficult cannulation ( $p = 0.076$ ) among others. PEP developed in 7 of the 192 individuals (3.6%), 6 PEP cases occurred in the indomethacin group and 1 in the epinephrine group ( $p = 0.016$ ). Univariate analysis of risk factors for PEP in patients with and without pancreatitis revealed no significant difference between the pancreatitis group and the non-pancreatitis group. **Conclusion:** In comparison to the administration of indomethacin alone, a single application of epinephrine and the combination of epinephrine and indomethacin seem to be effective in reducing the cases of PEP. A further randomized clinical trial with a larger sample size is required to confirm the efficacy of our medication in the prevention of pancreatitis after ERCP.

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## Introduction

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) [1]. The incidence of post-ERCP pancreatitis (PEP) ranges between 15 and 20% among patients at high risk of developing PEP [2, 3]. The pathogenesis of acute pancreatitis is not clearly identified. It has been reported that an aberrant calcium signaling pathway and reactive oxygen species might lead to autodigestion of the pancreas by its own proteases [4]. Therefore, several studies were carried out to identify the mechanisms underlying PEP in high-risk patients. However, papillary edema has been the focal point [5, 6]. Many different approaches have been applied in order to reduce the risk of PEP in patients and several pharmacologic agents have been examined for their effect on reducing the incidence rate and severity of PEP. Among these prophylactic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), especially indomethacin and diclofenac, have previously been evaluated in several randomized controlled trials [7, 8]. Via inhibiting phospholipase A2 (PLA2), NSAIDs play a significant role in the prevention of acute pancreatitis [9]. Other pharmacologic agents have also been evaluated for their prophylactic effects on PEP including protease inhibitors such as gabexate, ulinastatin, and nafamostat mesylate [10–12] and vasoactive mediators including lidocaine, nifedipine, epinephrine, and glyceryltrinitrate [5, 13–16]. The efficacy of indomethacin in the prevention of pancreatitis after ERCP is rather debatable with some studies supporting its significant role in reducing the severity and incidence of pancreatitis [7, 17–19], while others indicated the lack of any improvement in the case of indomethacin administration [20–22]. On the other hand, topical pharmacologic

agents have had some benefits over other interventions. In this regard, the role of local administration of epinephrine on reducing the incidence and severity of PEP has been reported in several studies [5, 15, 23]. The objective of this prospective randomized trial study was to evaluate whether or not the combination of indomethacin and epinephrine in comparison to the single administration of indomethacin differs in the pathogenesis and prevention of PEP.

## Patients and Methods

This study was designed as a randomized, prospective, double-blind trial. Informed consent was obtained from all individuals and the research proposal was approved by the ethics committee of the Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. From April 2013 to October 2014, patients who referred to the Endoscopy Unit of Taleghani Hospital for ERCP were recruited into this prospective study. A total of 293 patients underwent therapeutic ERCP; however, 101 patients were excluded from the study according to our exclusion criteria. Ultimately, 192 patients (98 male and 94 female) were included in this study. The age of the individuals ranged between 18 and 89 years. The mean age of patients was  $59.06 \pm 16.049$  years. The demographic characteristics of the patients in this study are shown in Table 1. Exclusion criteria were as follows: the pancreatic duct (PD) stent placement, history of acute pancreatitis, age under 18 years, prior endoscopic sphincterotomy, chronic pancreatitis with an acute exacerbation, an elevated serum amylase or lipase level (more than the upper normal limit:  $>100$  and  $>60$  IU/L, respectively), and an allergy to epinephrine. Patients who fulfilled the inclusion criteria were randomized into study groups. High-risk patients were defined as follows: suspected sphincter of Oddi dysfunction (SOD), precut biliary sphincterotomy, PD cannulation (at least once), endoscopic balloon dilation (after sphincterotomy), and the presence of more than two of the other risk factors including female sex, age  $<40$  years, nondilated common bile duct (CBD), normal bilirubin, and difficult cannulation [24].

### Study Design

The patients were randomized in a double-blinded manner into 3 groups: the epinephrine group (group A), the indomethacin group (group B), and the combined epinephrine and indomethacin group (group C). Randomization and administration of epinephrine or indomethacin were done by personnel who were not involved in the endoscopic procedure. The allocation was done using the random number generated by a computer. Each patient had a number corresponding to these random numbers and they were included in their specific group by this pattern. During the procedure, patients randomly received a spray of 10 ml epinephrine (diluted to 1/10,000 in saline) on the major papilla (immediately after ERCP) and a suppository placebo tablet (group A) or a suppository containing 100 mg of indomethacin (immediately after procedure) and normal saline solution sprayed on the major papilla (group B), or a combination of epinephrine on the major papilla and administration of 100 mg of indomethacin (group C). After the procedure, patients were evaluated for the PEP development.

### Definition of PEP

Serum amylase and lipase concentrations were measured and recorded before ERCP, 4 and 24 h after ERCP as indicated in Table 1. PEP was defined as an elevation of serum amylase levels more than threefold of the upper normal limit associated with at least two clinical symptoms including abdominal pain or tenderness, backache, nausea, and vomiting. The normal upper limit of serum amylase is 100 IU/L. The severity of PEP was classified as mild, moderate, or severe according to consensus classification [25]. We included patients with suspected SOD and we did not use manometry for the definition of SOD. Patients were prospectively evaluated for the occurrence of PEP between the groups.

### Statistical Analysis

All quantitative variables were indicated as mean  $\pm$  SD. The 3 groups were evaluated for statistical analysis. For the continuous variables, the analysis of variance was performed and the comparison between the groups was also assessed by the  $\chi^2$  test or the Fisher exact test. A *p* value of less than 0.05 was considered a statistical significance between the groups. According to Sotoudehmanesh et al. [7], in the case of any significant effect, relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) were computed with their 95% CI.

## Results

During 2013–2014, 293 patients underwent therapeutic ERCP; however, 101 patients were excluded from the study according to our exclusion criteria: prior endoscopic sphincterotomy (*n* = 6–8), PD stent placement (*n* = 9), history of acute pancreatitis (*n* = 7), age under 18 years (*n* = 6), chronic pancreatitis with an acute exacerbation (*n* = 5), an elevated serum amylase or lipase level (more than the upper normal limit: >100 and >60 IU/L, respectively) (*n* = 4), and an allergy to epinephrine (*n* = 2). Ultimately, 192 patients were recruited. During the ERCP, among 192 patients, 66 were randomized to the epinephrine group (group A), 68 to the indomethacin group (group B), and 58 to the combined indomethacin-epinephrine group (group C) (Fig. 1). The mean age of patients in the epinephrine group was  $59.59 \pm 15.680$  years, in the indomethacin group it was  $58.06 \pm 17.125$  years, and in the combination group it was  $59.62 \pm 15.369$  years.

### Procedure Outcomes

In the present study, we did not observe a significant difference between the 3 groups in sex, age, pre-ERCP amylase, lipase, PD dilation (*p* = 0.404), PD cannulation (*p* = 0.329), difficult cannulation (*p* = 0.076), sphincterotomy (*p* = 0.421), needle knife precut (*p* = 0.610), PD injection (*p* = 0.687), balloon dilation of sphincter of Oddi (*p* = 0.533), biliary stricture (*p* = 0.712), biliary duct tumor (*p* = 0.389), peri-ampullary diverticulum (*p* = 0.872), and suspected SOD (*p* = 0.808). In this study, PEP developed in 7 of the 192 individuals (3.6%), 6 PEP occurred in the indomethacin group and 1 case in the epinephrine group. However, none of the patients in the combination group (epinephrine and indomethacin) developed pancreatitis (*p* = 0.016) (Table 2). Univariate analysis of risk factors for PEP in patients with and without pancreatitis is presented in Table 3. In this study, there was no death due to pancreatitis

in the related patients. There was no significant difference between the pancreatitis group and the non-pancreatitis group according to PD dilation (0.739), suspected SOD (0.739), cholecystectomy (0.581), CBD stone (0.355), difficult cannulation (0.343), sphincterotomy (0.134), needle knife precut (0.403), PD cannulation (0.368), PD injection (0.798), balloon dilation of the sphincter of Oddi (0.419), CBD dilation (0.571), biliary stricture (0.330), biliary duct tumor (0.462), and peri-ampullary diverticulum (0.571) (Table 3).

## Discussion

Several pharmacologic components and endoscopic interventions have been utilized in order to prevent PEP. These are including anti-secretory agents, sphincter relaxants, anti-inflammatory agents, antioxidants, and protease inhibitors among others. Among these agents, however, indomethacin as a safe, inexpensive, available, easy-to-administer agent, which is associated with few side effects, has been shown to be effective in reducing the severity of PEP in previous studies [17–19, 26, 27], whereas a number of other studies indicated a null effect of indomethacin in preventing PEP [20–22, 28]. On the other hand, topical application of epinephrine as a vasoactive mediator has been reported to reduce PEP via decreasing the papillary edema. Lately, combination therapy has been emerged as an efficacious approach in preventing PEP [29–31]. In this prospective randomized trial study, we evaluated whether or not the combination of indomethacin and epinephrine differs in the pathogenesis and prevention of PEP. In our study, we found that among 68 patients in the indomethacin group, 6 individuals developed pancreatitis; however, in the epinephrine group only 1 patient developed pancreatitis (1/66). Among the 58 patients who received the combination medication, none developed pancreatitis. To our knowledge, this is the first report of epinephrine and indomethacin combination efficacy in preventing PEP. According to our findings, we observed that the single application of epinephrine and the combination of epinephrine and indomethacin significantly reduced the risk of PEP ( $p = 0.016$ ). The ERCP procedure might result in local or systemic inflammatory response, which is the precursor of PEP [32–34]. Furthermore, PLA2 has a vital role in the development of this inflammatory response [33]. It has been demonstrated that the mechanisms of NSAIDs in the prevention of PEP is to suppress peculiar molecular pathways that contributed to prostaglandin synthesis, PLA2, and neutrophil-endothelial cell attachment [33]. Indomethacin as an important inhibitor of PLA2 and its role in the prevention of PEP has been evaluated in several previous studies [7, 18, 19, 27]. In line with our study, Elmunzer et al. [35] evaluated the efficacy of rectal indomethacin on 602 patients who underwent ERCP. They observed that rectal indomethacin significantly decreased the PEP incidence and severity. Among 79 patients who developed pancreatitis, 27 (9.2%) were in the indomethacin group. However, in our study, the majority of patients who developed pancreatitis (6/7) were in the indomethacin group, and in comparison to the application of indomethacin and epinephrine combination, patients were at high risk of developing PEP ( $p = 0.016$ ). In contrast to our study, a meta-analysis by Yaghoobi et al. [19] showed that rectal administration of indomethacin significantly decreased the PEP risk to half in related patients. In another study on the Iranian population, Sotoudehmanesh et al. [7] reported that administration of rectal indomethacin reduced the risk of PEP ( $p = 0.01$ , RRR = 88%, ARR = 0.16, NNT = 6). However, the recent study by

Döbrönte et al. [20] revealed no benefit in the rectal application of indomethacin in reducing the incidence of PEP. This is consistent with their previous findings on 228 patients who underwent ERCP [21]. In our study, we excluded patients who underwent the placement of a stent in order to get a precise effect of the medication after the ERCP. There have been numerous studies that evaluated the efficacy of pancreatic duct stent placement and the prevention of PEP [36–38]. However, pharmacological agents have several benefits over stents including the cost benefit, ease of administration, minimal side effects, and widespread availability. Thus, despite the high efficacy of pancreatic stenting placement, it is not performed widely and one fifth of specialists prefer not to place pancreatic stents in any condition [39]. On the other hand, in an ad hoc analysis, Elmunzer et al. [40] showed that rectal indomethacin could replace PD stent placement in high-risk cases and a meta-analysis by Puig et al. [27] revealed that NSAIDs were effective either in the absence or presence of a pancreatic stent. The topical application of epinephrine and its role in the prevention of PEP has also been evaluated in several previous studies [5, 41, 42]. Matsushita et al. [5] observed that among 370 patients undergoing diagnostic ERCP, PEP developed in 4 cases (1.1%) in the control group, whereas no PEP occurred in the epinephrine group (0/185) ( $p = 0.1230$ ); they found that epinephrine sprayed on the papilla tended to reduce PEP; however, it was not statistically significant. One of the vital roles of epinephrine is the ability to decline edema and pancreatic ductal outflow obstruction, which is associated with the pathogenesis and progression of PEP [1–4]. In another valuable study, Xu et al. [42] evaluated the efficacy of epinephrine in a series of 461 patients and observed that PEP occurred in 9/461 individuals (6.45%); however, the incidence rate was higher in the control group (31/480, 1.95%). Therefore, applying epinephrine was a promising approach and reduced the incidence of pancreatitis after ERCP ( $p = 0.0086$ ). A valuable meta-analysis by Akshintala et al. [41] evaluated the efficacy of several pharmacological agents for the prevention of PEP including NSAIDs, topical epinephrine, antibiotics, and nafamostat. They observed that in comparison to other agents, topical epinephrine had the most effect on reducing PEP with 85.9% followed by rectal NSAIDs with 58.1%. In the present study, there were some limitations: first, the patients included in this study were recruited from a single center; however, a multi-institutional registry is required to confirm our findings on combination efficacy of epinephrine and indomethacin. Second, due to our small sample size, we could not evaluate the effect of the putative medications on the severity of PEP in our patients.

## Conclusion

In comparison to the administration of indomethacin alone, the combination of epinephrine and indomethacin seems to be effective in reducing PEP. A further randomized clinical trial with a larger sample size is required to confirm the efficacy of our medication in the prevention of pancreatitis after ERCP.



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## Statement of Ethics

Informed consent was obtained from all individuals and the research proposal was approved by the ethics committee of the Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

## Disclosure Statement

The authors declare no conflicts of interest.

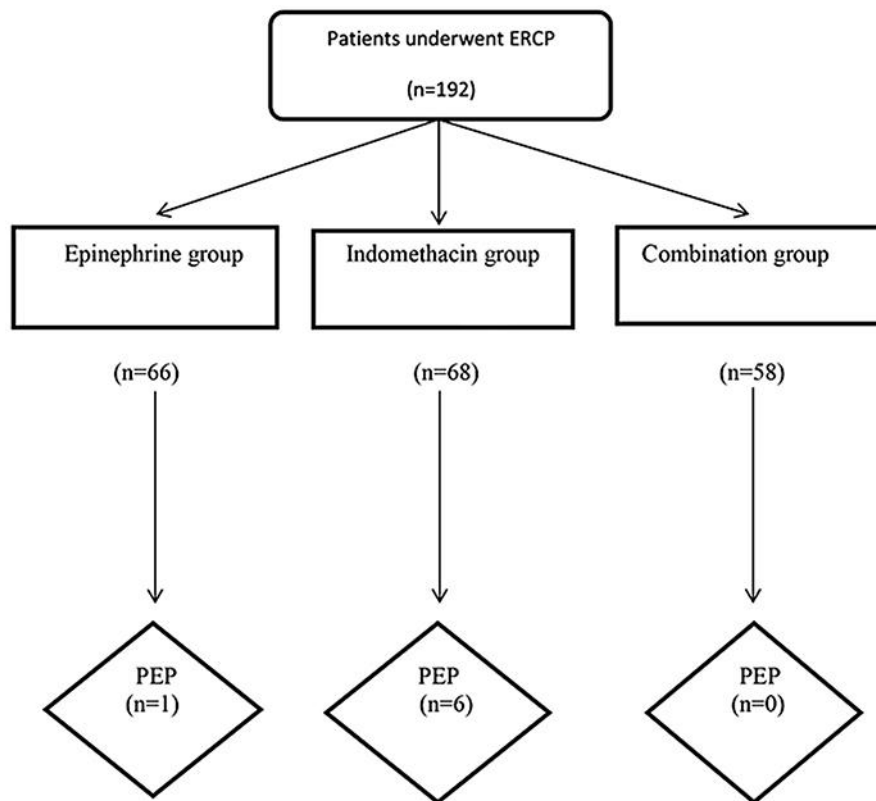
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**Fig. 1.** Flowchart of patients through the clinical protocol. PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis.

**Table 1.** Demographic and clinical characteristics of patients undergoing ERCP

	Epinephrine <i>n</i> (%)	Indomethacin <i>n</i> (%)	Combination <i>n</i> (%)	<i>p</i> value
Male	33 (33.7)	41 (41.8)	24 (24.5)	0.104
Female	33 (35.1)	27 (28.7)	34 (36.2)	
Mean age, years	59.59±15.680	58.06±17.125	59.62±15.369	0.818
PD dilation	1 (12.5)	4 (50.7)	3 (37.5)	0.404
CBD stone	28 (34.1)	30 (36.6)	24 (29.3)	0.970
PD injection	2 (33.3)	3 (50.0)	1 (16.7)	0.687
PD cannulation	6 (50.0)	2 (16.7)	4 (33.3)	0.329
CBD dilation	48 (37.5)	45 (35.2)	35 (27.3)	0.343
Balloon dilation of sphincter of Oddi	16 (42.1)	12 (31.6)	10 (26.3)	0.533
Biliary stricture	13 (40.6)	10 (31.2)	9 (28.1)	0.712
Biliary duct tumor	3 (18.8)	7 (43.8)	6 (37.5)	0.389
Suspected SOD	3 (37.5)	2 (25.0)	3 (37.5)	0.808
Difficult cannulation	14 (25.0)	19 (33.9)	23 (41.1)	0.076
Sphincterotomy	51 (33.1)	53 (34.4)	50 (32.5)	0.421
Needle knife precut	7 (30.4)	7 (30.4)	9 (39.1)	0.610
Peri-ampullary diverticulum	17 (34.7)	16 (32.7)	16 (32.7)	0.872
Cholecystectomy	13 (34.2)	13 (34.2)	12 (31.6)	0.976
Pre-amylase level, IU/L	88.4 (40.25)	98 (43.2)	96 (45.62)	0.732
Pre-lipase level, IU/L	101 (51.40)	92.5 (46.9)	90.1 (41.85)	0.605
Post-amylase level (4 h), IU/L	264.5 (255.1)	286.3 (274.5)	269.1 (257.6)	0.460
Post-amylase level (24 h), IU/L	642.1 (1,115)	676 (1,163.3)	615.4 (1,064.2)	0.542

ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct; CBD, common bile duct; SOD, sphincter of Oddi dysfunction.

**Table 2.** Outcomes of patients after endoscopic retrograde cholangiopancreatography

	Epinephrine <i>n</i> (%)	Indomethacin <i>n</i> (%)	Combination <i>n</i> (%)	<i>p</i> value
Pancreatitis				
Mild	1 (20)	4 (80)	0 (0.0)	0.016
Moderate	0 (0.0)	1 (100)	0 (0.0)	
Severe	0 (0.0)	1 (100)	0 (0.0)	

**Table 3.** Univariate analysis of risk factors for post-ERCP pancreatitis in patients with and without pancreatitis

	Non-pancreatitis group, n (%)	Pancreatitis group, n (%)	Total (n = 704) n (%)	p value
PD dilation	8 (100)	0 (0)	8 (100)	0.739
Suspected SOD	8 (100)	0 (0)	8 (100)	0.739
Cholecystectomy	37 (97.4)	1 (2.6)	38 (100)	0.581
CBD stone	80 (97.6)	2 (2.4)	82 (100)	0.355
Difficult cannulation	130 (95.6)	6 (4.4)	136 (100)	0.343
Sphincterotomy	150 (97.4)	4 (2.6)	154 (100)	0.134
Needle knife precut	23 (100)	0 (0.0)	23 (100)	0.403
PD cannulation	11 (91.7)	1 (8.3)	12 (100)	0.368
PD injection	6 (100)	0 (0)	6 (100)	0.798
Balloon dilation of sphincter of Oddi	36 (94.7)	2 (5.3)	38 (100)	0.419
CBD dialation	123 (95.4)	5 (4.6)	128 (100)	0.571
Biliary stricture	30 (93.8)	2 (6.2)	32 (100)	0.330
Biliary duct tumor	15 (93.8)	1 (6.2)	14 (100)	0.462
Peri-ampullary diverticulum	47 (95.9)	2 (4.1)	49 (100)	0.571
Medication				
Epinephrine	66 (100)	0 (0.0)	66 (100)	0.016
Indomethacin	62 (91.2)	6 (8.8)	68 (100)	
Combination	57 (98.3)	1 (1.7)	58 (100)	

ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct; CBD, common bile duct; SOD, sphincter of Oddi dysfunction.