Original Article

Administration of Rectal Diclofenac before, Compared with before-after Endoscopic Retrograde Cholangiopancreatography to Prevent Pancreatitis; a Double-Blind Randomized Controlled Trial

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ABSTRACT

Background:
Acute pancreatitis is one of the most common complications following endoscopic retrograde cholangiopancreatography (ERCP), which can be life-threatening if the treatment is postponed. This study aimed to evaluate the effect of non-steroidal anti-inflammatory drugs (suppository diclofenac) on preventing post-ERCP pancreatitis (PEP).

Materials and Methods:
In this double-blind, randomized clinical trial, 219 patients referred to our ERCP unit who passed inclusion and exclusion criteria were randomly assigned to two groups: group A (103 patients) received a diclofenac suppository 30 minutes before and immediately after ERCP. In Group B (116 patients), a diclofenac suppository was prescribed only before the procedure. Patients were evaluated regarding clinical signs and symptoms of pancreatitis for 24 hours. Also, serum amylase level was checked at baseline, 6, and 24 hours after the procedure.
The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences (IR.IUMS.FMD.REC.1399.190). Also, the study protocol was registered in the Iranian Registry for Clinical Trials (IRCT20191231045969N2).

Results:
The PEP was seen in three patients in group A and seven patients in group B, which was not significantly different ($P=0.341$). The severity of pancreatitis was mild in all patients except one in group B, who developed moderate PEP. Moreover, in 97.71 % of cases, ERCP was successful for the first time, and in 94.18 % of group A and 89.66% of group B, no complications of bleeding or perforation were detected.

Conclusion:
Administration of rectal diclofenac before and after ERCP had no significant effect on the prevention of pancreatitis compared with pre-ERCP administration.

Keywords: Pancreatitis; Diclofenac; NSAIDs; Endoscopic retrograde cholangiopancreatography; Randomized controlled trial

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INTRODUCTION

Many studies have been performed on factors that affect the probability of adverse events after endoscopic retrograde cholangiopancreatography (ERCP). Common adverse events of ERCP include pancreatitis, bleeding, perforation, infection, and cardiovascular problems (1). Pancreatitis has been mentioned as the most prevalent one, with a prevalence of 5% to 15% in different studies or 1% to 40% according to a meta-analysis based on various factors. The main mechanism of developing post-ERCP pancreatitis has not been fully understood, but it seems to be multifactorial. Mechanical damage, chemical and enzymatic factors, physician's experience, and the complexity of the underlying disorder are effective (2). Pharmacological and non-pharmacological methods have been used to prevent pancreatitis. Non-pharmacological modalities include pancreatic duct stenting, which has limited applications due to their high cost and the need for sufficient skill to place them. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for the prevention of PEP with controversial outcomes (3). However, ERCP elicits an inflammatory response, especially through phospholipase A2, which can be inhibited by NSAIDs at least theoretically (4).

On the other hand, some research shows that the administration of rectal NSAIDs such as diclofenac (5), and indomethacin (6) before and/or after the ERCP procedure is useful in preventing post-ERCP pancreatitis (PEP). Diclofenac is a potent inhibitor of the cyclo-oxygenase enzyme. The enzyme cyclo-oxygenase converts arachidonic acid to prostaglandins. There are at least two cyclo-oxygenase isoforms called Cox-1 and Cox-2. It inhibits the production of prostaglandins and thromboxane by inhibiting cyclo-oxygenase, thus demonstrating its analgesic and inflammatory effects. Recent studies have shown that NSAIDs administration before ERCP reduces the risk of post-ERCP pancreatitis (7). On the other hand, because NSAIDs are inexpensive, low-risk, and easily available, they are considered a suitable option for the prevention of pancreatitis following ERCP. Due to controversial reports available in the literature, we aimed to determine and compare PEP in patients receiving rectal diclofenac before and after ERCP with those who received rectal diclofenac just before ERCP.

The diagnosis of post-ERCP pancreatitis (PEP) is generally made in patients who develop new or worsening abdominal pain within 24 hours after ERCP and have more than three times the normal level of amylase or lipase, which prolongs the hospital stay (8).

METHODS AND MATERIALS

Study participants and randomization

Between 23 September 2019 and 30 November 2020, 366 patients who were a candidate for ERCP in Firoozgar hospital in Tehran, Iran, were recruited in this randomized controlled trial study, but 138 were excluded before randomization (Figure 1). All the exclusion criteria are reported in Table 1.

Patients were randomly divided into two groups using the random blocked method: A and B groups. The researcher and patients were unaware of patients' allocation. This was a double-blind RCT study that is handled by the nurse, who is the only person involved in the allocation process.

Group A, the intervention group, was supposed to receive a 100 mg rectal diclofenac within 30 minutes before and immediately after the ERCP procedure. While in group B, the control group, the diclofenac suppository was prescribed only within 30 minutes before the procedure. In other words, all the patients in both groups, intervention (group A) and control (group B), received one dose of 100 mg rectal diclofenac before the ERCP. Meanwhile, group A also received their second dose immediately after the ERCP procedure while they were anesthetized. So, due to the anesthetized condition, the patients did not know about the second dose treatment and could not recognize whether they were in groups A or B. As a result, it was supposed not to use any placebo.

The patients entered into the study could be computed according to the occurrence probability of both control (P_0), and intervention groups (P_1), probability of type I error (a), and safety factor (Z)=(1-a):

$$n=\frac{\left[Z_{1-\frac{\alpha}{2}}\sqrt{2\bar{P}\left(1-\bar{P}\right)}+Z_{1-\beta}\sqrt{P_0\left(1-P_0\right)+P_1\left(1-P_1\right)}\right]}{\left(P_1-P_0\right)^2} \quad (1)$$

where:

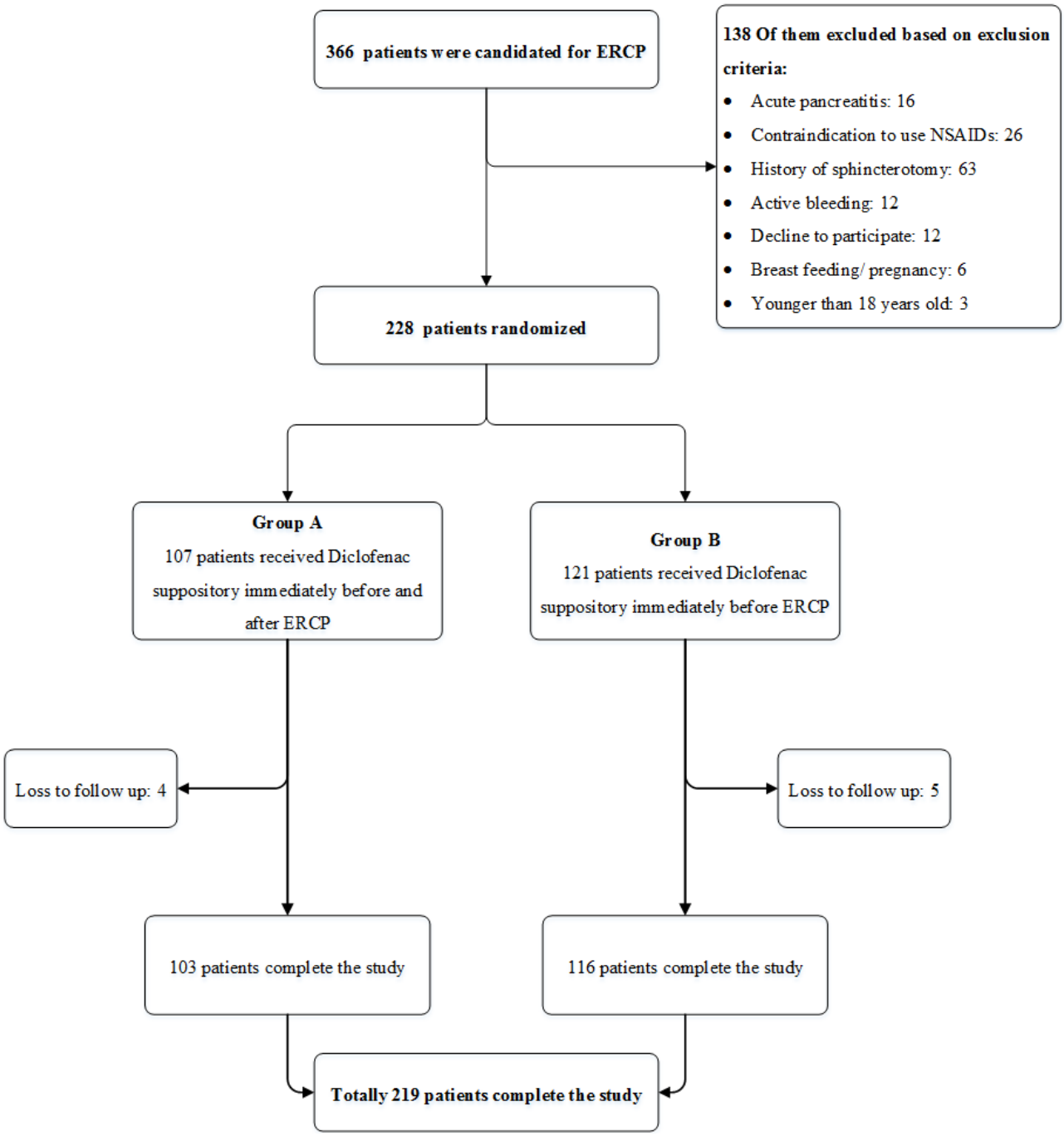

Figure 1: RCT flowchart

$$\bar{P} = \frac{P_0 + P_1}{2} \qquad (2)$$

Based on Ref. (9), $P_0 = 0.095$ and $P_1 = 0.048$. Therefore, the number of patients would be 51 using Eq.(1). However, to cover any probably withdrawn patients during the trial and ensure the results of statistical analysis, the number of patients in the intervention group (group A) and control group (group B) were considered 103 and 116, respectively, which form a statistical society

population of 219 patients (allocation ratio approximately 1:1).

It is worth noting that for 79 cases, although sphincterotomy was performed, some sludges were extracted and due to pure drainage, a plastic PD stent placement was performed. So, biliary drainage was created. Finally, the PD stent was removed after several next days.

Intervention

Group A, the intervention group, was supposed to receive a 100 mg diclofenac suppository within 30 minutes before and immediately after the ERCP procedure. While in group B, the control group, a diclofenac suppository was prescribed only within 30 minutes before the procedure. Personal and baseline clinical characteristics of all patients were recorded using a researcher-made questionnaire including the information noted in Table 2.

Table 1. Exclusion criteria for the randomized controlled trial

No	Criteria
1	Not giving informed consent
2	Younger than 18 years old
3	History of sphincterotomy
4	Evidence of acute pancreatitis
5	Having contraindications to the use of diclofenac (renal failure, liver failure, history of drug allergy, severe cardiovascular diseases, active bleeding)
6	Pregnancy and breastfeeding
7	Serum amylase level higher than 200 U/l at baseline

Table 2. Questionnaire information

No	Info
1	Age
2	Sex
3	History of medical illness
4	Serum amylase level
5	Abdominal pain
6	Clinical pancreatitis signs and symptoms
7	The severity of clinical pancreatitis
8	Length of hospital stay
9	ERCP indications (suspected malignancy, calculus, primary sclerosing, cholangitis)
10	Sphincterotomy

The patients were also evaluated for up to 24 hours regarding the clinical sign and symptoms of pancreatitis and laboratory findings and were visited by a resident of internal medicine and examined regarding possible adverse events.

Outcomes

The primary outcome was evaluating acute PEP based on new-onset upper abdominal pain and elevation of serum amylase level more than three times the institutional upper limit of normal (according to Atlanta classification) (10). The normal serum amylase level is about 92 U/l in our medical center. Secondary endpoints were assessing the severity of PEP based on Cotton criteria (11), ERCP-related adverse events including bleeding and perforation, and length of hospital stay.

Ethical consideration

Written informed consent was obtained from all patients before participating in the study. All possible side effects were explained. All the steps of the study were performed according to the Helsinki declaration. The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences (IR.IUMS.FMD.REC.1399.190). Also, the study protocol was registered in the Iranian Registry for Clinical Trials (IRCT20191231045969N2).

Statistical analysis

Numeric data were reported as mean ± standard deviation (SD) and categorical data as frequency. The data were analyzed using SPSS software version 16 (SPSS Inc., Chicago, Ill., The USA). Chi-square, *t*-test, ANOVA, or Fisher exact test were used when appropriate. A P-value below 0.05 was considered statistically significant.

RESULTS

Finally, 219 patients completed the study. 103 out of 107 patients in group A received a diclofenac suppository 30 minutes before and immediately after ERCP (four patients in group A lost the study), and 116 out of 121 patients in group B received diclofenac only 30 minutes before the procedure (five patients in group B lost the study). Age and sex distribution did not differ significantly between

the groups. Most of the patients in each group (group A: 74 (71.84%), group B: 82 (70.68%) did not have any underlying diseases. Also, the mean hospital stay in both groups was almost the same. Table 3 summarizes the comparison of baseline characteristics between the groups. Overall, 206 (94.1%) patients had no abdominal pain or clinical symptoms after the procedure. Clinical, laboratory and study outcomes have been summarized in Table 4.

In addition to Table 3, the two groups were compared based on the sphincter of Oddi dysfunction (SOD). Group A contained six SOD cases (5.82%), while group B contained seven SOD cases (6.03%). Based on Fisher's exact test, the *P*-value of the SOD factor is about $1 > 0.05$, which means it has not played as a confounding factor between the two groups.

In the current study, the influence of three factors including female sex, history of post-ERCP pancreatitis, and PD stent insertion were evaluated for post-ERCP pancreatitis. The results are reported in Table 5. According to Table 5, female sex and PD stent insertion with $P > 0.05$ were not considered risk factors for PEP. This result was also reported by Ref (9).

Table 3. Comparing baseline characteristics between groups

Variables	Group A (n=103)	Group B (n=116)	*P*-value
Age (Years)	56.47±12.87	58.03±13.13	0.750
Sex (Male)	49 (47.57)	60 (51.72)	0.589
Past medical history			
None	74 (71.84)	82 (70.68)	0.882
DM	4 (3.88)	7 (6.03)	0.546
HTN	16 (15.53)	18 (15.51)	0.981
IHD	2 (1.94)	4 (3.44)	0.686
Others	7 (6.79)	5 (4.31)	0.555
ERCP indications			
CBD Stone	74 (71.84)	82 (72.41)	0.882
Malignancy	26 (25.24)	30 (25.86)	0.963
PSC	1 (0.9)	3 (2.58)	0.624
Cholangitis	2 (1.94)	1 (0.9)	0.602
Baseline serum amylase level (U/l)	68.72±35.39	76.17±39.16	0.278

Data expressed as frequency (proportion) or mean±standard deviation.
ERCP: Endoscopic retrograde cholangiopancreatography; DM: Diabetes; HTN: Hypertension; IHD: Ischemic heart disease; CBD: Common bile duct; PSC: Primary sclerosing cholangitis.

In addition, 10 (4.56%) participants developed pancreatitis, three in group A and seven in group B, which was mild in most patients (9 cases out of 10). Using a suppository before and after ERCP compared with a single use did not significantly alter the adverse event of ERCP ($P=0.32$). There was also no significant difference in the hospital stay between the two groups ($P=0.58$).

Furthermore, age and sex were not associated with an increased risk of post-ERCP abdominal pain, amylase level, or pancreatitis. On the other hand, underlying diseases were not associated with an increased risk of abdominal pain after the procedure, although underlying diseases did not increase the risk of hospital stay.

DISCUSSION

A randomized controlled trial was conducted to investigate the influence of using diclofenac suppositories before ERCP and before-after ERCP procedures for PEP prevention. 219 patients were divided blindly into two intervention (n=103) and control (n=116) groups.

In our study, 4.56% of the patients experienced post-ERCP pancreatitis, which is close to the results of Lai and colleagues (5.6%) (9). The small difference between the results may be caused by the more patients referring to our endoscopy center per year, which justifies the quite low rate of PEP.

The post-ERCP pancreatitis was diagnosed by serum amylase level and abdominal pain. No significant difference in amylase level was observed between the two groups A and B ($P>0.05$). I.g., the 6h (6 hours) amylase level was a little lower in group A (202.57±290.25 U/l) compared with group B (251.88±470.12 U/l) with *P*-value=0.36. While the 24h (24 hours) amylase level was a little higher in group A compared with group B with *P*-value=0.67. Also, the other PEP criteria, abdominal pain, had no considerable difference between the two groups (4.85% for group A and 6.89% for group B) with a *P*-value>0.05. As a result, both groups had approximately the same experience.

Both groups experienced almost the same admission duration. So, using a diclofenac suppository before and immediately after ERCP had no extra effect on

Table 4. Comparing study outcomes between the groups

		Group A (n=103)	Group B (n=116)	*P*-value
Pancreatitis				
Yes		3 (2.9)	7 (6.0)	0.341*
No		100 (97.1)	109 (94.0)	
Serum amylase level (U/l)				
	6 hours after ERCP	202.57±290.25	251.88±470.12	0.36¶
	24 hours after ERCP	269.01±487.73	242.17±443.23	0.67¶
Abdominal pain during 24 hours after ERCP		5 (4.85)	8 (6.89)	0.52**
Hospital stays (days)		5.02±3.05	5.25±3.19	0.58¶
ERCP canalization				
	Successful for the first time	101 (98.05)	113 (97.41)	0.78*
	Successful for the 2nd time	2 (1.94)	3 (2.58)	
Adverse events				
	None	97 (94.17)	104 (89.65)	
	Bleeding	2 (1.94)	2 (1.72)	0.32*
	Perforation	4 (3.88)	10 (8.62)	
PD stent insertion				
	No	63 (61.16)	77 (66.37)	0.48**
	Yes	40 (38.83)	39 (33.62)	

Data expressed as frequency (proportion) or mean±standard deviation; *Fisher's exact test; **Chi-square test; Independent sample *t*-test , ERCP: Endoscopic retrograde cholangiopancreatography; PD: Pancreatic duct.

Table 5. Risk factors evaluation for post-ERCP pancreatitis

Item	PEP (n=10)	Non-PEP (n=209)	*P*-value	OR (95% CI)
Female	6	104	0.748	1.51 (0.42-5.52)
PD stent insertion	2	77	0.336	0.43 (0.09-2.07)

hospitalization duration compared with using a diclofenac suppository just before ERCP ($P=0.58$).

Putting a PD stent can prevent PEP significantly. However, it was tried to use a PD stent in both groups A and B with approximately the same occurrence percentage (38.83% for group A and 33.62% for group B). The statistical results reveal that putting a PD stent did not act as a confounding factor between the two groups A and B, i.e. the *P*-value of this factor is 0.48 which is much higher than 0.05. Based on the results of Table 5, among all 79 cases of using PD stent, just two cases suffered from PEP ($P=0.336$), which means that it is a successful method to prevent PEP. It is worth noting that in Ref (9), the stent was used for 30 cases out of 162 cases (21.8% and 14.7% for groups A and B, respectively). They reported just two PEP occurrences after using a stent with a *P*-value=0.521, which is close to our results.

In our study, the incidence of PEP was not different between the two groups; therefore, the use of a PD stent has not played a role as a confounding factor. ERCP elicits an inflammatory response, especially through phospholipase A2. Phospholipase A2 and cyclo-oxygenase play an essential role in the pathogenesis of acute pancreatitis, and NSAIDs might act to inhibit these factors. Besides, meta-analyses published by Sotoudehmanesh and colleagues (12) and Elmunzer and co-workers (13) showed the efficacy of rectal diclofenac or indomethacin in reducing the incidence of post-ERCP pancreatitis.

However, based on our experiences and practices and also due to the lower occurrence of PEP in the intervention group who were treated with rectal diclofenac before and after ERCP, we deeply suggest using double dose rectal

diclofenac before and immediately after ERCP to prevent the post pancreatitis.

In a study conducted by Zhao Hau Lai and colleagues on 162 patients, the effect of suppository NSAIDs was assessed on the incidence of pancreatitis (9). In the control group, patients received NSAID suppositories before ERCP, and in the intervention group, they received suppositories before and after ERCP. The researchers reported that the incidence of pancreatitis in the intervention group was lower than in the control group (8.4% vs. 5.9%), but no statistically significant difference was observed. This is in line with our results indicating the efficacy of suppository NSAIDs in preventing post-ERCP pancreatitis.

On the other hand, Young Koog Cheon and co-workers examined the efficacy of oral diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients (7). They claimed that prophylactic diclofenac could not decrease the frequency or severity of post-ERCP pancreatitis. This is against our results, which might be due to different study populations or routes of drug administration. Oral consumption might decrease the plasma concentration of the drug due to the first-pass effect, which is not seen in the rectal route. This might justify the difference between this investigation and our results.

To address the limitations in our study, it is suggested to investigate the influence of different routes, dosages, different NSAIDs, or a combination of different NSAIDs. Furthermore, it seems that underlying diseases such as cholangitis might affect the probability of PEP. It is suggested to perform more extensive studies, including patients without any underlying diseases (such as common bile duct stones and otherwise healthy to elucidate the exact role of NSAIDs in the prevention of PEP.

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AUTHORS' CONTRIBUTION
All the authors listed above were quite equally involved in preparing the manuscript.

CONFLICT OF INTEREST
The authors declare no conflict of interest related to this work.

FINANCIAL DISCLOSURE
None.

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