



**IMPACT OF RECTAL DICLOFENAC IN PREVENTING POST ENDOSCOPIC  
RETROGRADE CHOLANGIO PANCREATOGRAPHY PANCREATITIS: A  
RANDOMIZED PROSPECTIVE STUDY**

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**ABSTRACT**

**Introduction:** There is a conflict regarding the efficacy of diclofenac in reducing the frequency of post ERCP pancreatitis. There was a need to conduct this study in the local population so that this conflict could be resolved which can help us in opting diclofenac in regular use among the patients undergoing ERCP to prevent pancreatitis associated with it. The aim of our study was to compare the frequency of pancreatitis in post endoscopic retrograde cholangiopancreatography patients treated with and without diclofenac suppositories. **Methods:** A total of ninety (n=90) patients of either gender between age 20-70 years who presented with radiologically proven stones in CBD were enrolled. Patients were randomly divided into 2 groups. Group A was administered per rectal 100 mg of diclofenac potassium and Group B was taken as a control group. All the patients underwent ERCP and were monitored for 48 hours for the diagnosis of post ERCP pancreatitis (PEP). **Results:** PEP was diagnosed in 17.8% (n=8/45) in group A patients while it was diagnosed in 44.4% (n=20/45) patients in group B (p=0.006). The efficacy of diclofenac potassium was significantly better among males with shorter duration of the procedure (P<0.05). No other statistical difference noted (P>0.05 in the rest of the cases). **Conclusions:** Efficacy of per rectal diclofenac potassium for prophylaxis of post-ERCP pancreatitis was significantly better when compared with the control group.

**KEYWORDS:** ERCP, Pancreatitis, PR Diclofenac, Nsaids.

**INTRODUCTION**

Endoscopic retrograde cholangiopancreatography (ERCP) is a combined endoscopic and fluoroscopic procedure in which an upper endoscope is led into the second part of the duodenum, making it possible for the passage of other tools via the major duodenal papilla into the biliary and pancreatic ducts. It is not only used as a diagnostic tool but also has a therapeutic role. It has become an important minimally invasive procedure to diagnose ampullary carcinomas and also for stent placement in patients with strictures, fistulae, leaks, or as a therapeutic tool for people who can't undergo surgery i.e patients with ampullary carcinomas. From a mere removal of stone to stenting, all this can be done through ERCP. However, complications directly attributed to ERCP are as high as 6.8%. And the incidence of post-ERCP pancreatitis (PEP) is 3.5%, making it the most

frequent complication following the procedure. Acute pancreatitis is the most common and can be fatal.<sup>[1]</sup>

Hence, there is a need to look out for medications and drugs which can be used prophylactically. Medications currently being used for prophylaxis include NSAIDs, nitroglycerin, somatostatin, octreotide, ceftazidime, and anti-protease drugs.<sup>[2]</sup> Studies have shown rectal NSAIDs to be most effective. Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A2, cyclooxygenase, and neutrophil-endothelial interactions, all believed to be involved in the pathogenesis of acute pancreatitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit enzymes, phospholipase A2, and cyclooxygenase, as well as neutrophil-endothelial interactions, which are known to be involved in the pathogenesis of acute pancreatitis.<sup>[3]</sup>

NSAIDs are an attractive option in the prevention of post-ERCP pancreatitis but there is a lot of heterogeneity. Studies from different corners of the world have shown different results.<sup>[4,5]</sup> So, in this RCT we make an effort to explore the conflict regarding the efficacy of NSAIDs; diclofenac in reducing the incidence of PEP. There is a need to conduct this study in the local population for us to better understand this drug so that we can prescribe diclofenac to the patients undergoing ERCP to prevent PEP. NSAIDs in the form of rectal suppositories have been widely used for this purpose. In the present experiment, we aimed to evaluate per rectal diclofenac potassium for the prevention of PEP.

## MATERIALS AND METHODS

This is a randomized, prospective study that was conducted at the Department of Gastroenterology, Holy Family Hospital, Rawalpindi, Pakistan from 16-03-2019 to 15-09-2019. The sample size was calculated with the help of WHO calculation, considering the level of significance, power of test, and anticipated population. The calculated sample size was 90. Patients of both gender with age in the range 20-70 who had a stone in CBD being radiologically proven on ultrasound, CT scan, or MRCP were included in our study. For Ultrasound having the echogenic focus of size range between 2 to 20mm or CBD >6mm+1mm per decade above the age of 60 years was taken as an indicator of stone in CBD. Exclusion criteria consisted of patients who: (1) Were Pregnant (2) had acute pancreatitis within the preceding two weeks before ERCP, (3) were currently being treated with loop diuretics, (4) allergic to diclofenac or other NSAIDs; (5) had contrast allergy, (6) had impaired renal function (serum creatinine > 2 mg/dL), (7) had known liver cirrhosis, (8) had undergone previous CBD stenting, (9) had a history of peptic ulcer, and (10) had coagulopathy disorders.

After approval from the ethical review committee of the hospital 90 patients who presented in the department of Gastroenterology, Holy Family Hospital, Rawalpindi fulfilling the above criteria were enrolled for the study. The patients were counseled and explained the detail of the study. Written informed consent was taken from patients. Upon presentation, detailed clinical history was taken along from each patient. All necessary investigations were done as per standard protocols. The sample was then divided into two groups. Group A (n=45) was the intervention group and group B (n=45) was a reference group.

100mg per-rectal diclofenac potassium was given to group A patients 30 minutes before starting the procedure, while group B did not receive per-rectal diclofenac potassium. All the ERCP's were performed by the same team of consultant doctors who were blinded about the study group. The patients were kept under observation for 48 hours after ERCP as per hospital protocol. Post ERCP serum amylase was done at 6, 24, 48 hours to rule out pancreatitis. The diagnosis of post

ERCP pancreatitis was made as per operational definition. The patient who developed post ERCP pancreatitis were managed as per standard protocol.

All the data was recorded into the attached performa along with the demographic details of the patient. The effect modifiers like age and gender were handled through consecutive sampling, followed by random allocation in two groups.

## DATA ANALYSIS PROCEDURE

Data was entered and analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0. (IBM Corp., Armonk, NY, US). Frequency and percentages were calculated for categorical data. For continuous data mean and standard deviation (SD) were calculated. The proportion of subjects who developed post ERCP pancreatitis in both groups was compared using the chi-square test or Fisher exact test (if the expected count was < 5 in any cell). P-value < 0.05 was taken as significant. Effect modifiers like age, gender, and duration were controlled by stratification. A post-stratification chi-square test was applied.

## RESULTS

### Demographic Characteristics of Enrolled Subjects

A total of ninety (n=90) patients of either gender between age 20-70 years who presented with radiologically proven stones in CBD were enrolled. Patients were randomly divided into 2 groups. Group A was administered per rectal 100 mg of diclofenac potassium and Group B was taken as a control group. All the patients underwent ERCP and were monitored for 48 hours for the development of post ERCP pancreatitis (PEP). Table 1 demonstrates the characteristics and demographics of patients.

**Table 1: Characteristics and demographic data of patients.**

Parameters	Sub-groups	Treatment group (n)	Placebo group (n)
	Number of pts	45	45
Sex	Male (n)	23	27
	Female (n)	22	18
Age groups	Mean age (years)	43.3	47.7
	20-45 years (n)	26	17
	46-70 years (n)	19	28
Duration	Mean (min)	39.1	45.6
	< 45 min (n)	33	26
	> 45 min (n)	12	19

**POST ERCP PANCREATITIS**

Only 18% of patients in Group A developed PEP as compared to group B where 44% (n=20/45) patients developed PEP. Efficacy of per rectal diclofenac potassium for prophylaxis of post-ERCP pancreatitis was significantly better when compared with control group.

**STRATIFICATION FOR EFFECT MODIFIERS**

Table 2 shows PEP data stratified with respect to age, gender and duration of procedure. The efficacy of per rectal diclofenac potassium was significantly better among males with shorter duration of procedure (P<0.05).

	Sub-groups	Treatment	Placebo	P-value
<b>PEP</b>		18%	44%	0.006
<b>PEP with stratification to gender</b>	males	22%	52%	0.029
	females	14%	33%	0.138
<b>PEP with stratification to age groups</b>	20-45 years	15%	41%	0.058
	46-70 years	21%	46%	0.076
<b>PEP with stratification to duration of procedure</b>	<45 min	9%	42%	0.003
	>45 min	42%	47%	0.756

**DISCUSSION**

The most common complication of ERCP is PEP (Post ERCP pancreatitis). In our study, the primary endpoint was the incidence of PEP in the control and treatment groups. We found that one dose of 100mg rectal diclofenac given 30 minutes before ERCP significantly reduced the incidence of post-ERCP pancreatitis in patients with choledocholithiasis. Moreover, we found that the efficacy of diclofenac potassium was substantially better among males and also among patients with a shorter duration of the procedure.

The best evidence on the use of NSAIDs for prevention of PEP came from two large meta-analyses published recently. In one meta-analysis Serrano JPR included 21 randomized controlled trials with a total of 6854 patients.

Pooled analysis showed that 7% of cases were diagnosed with PEP in the NSAIDs group and there were 12% cases in the placebo group. The risk for PEP was lower in the NSAID group (P <0.05). 11 studies of this meta-analysis used diclofenac, and PEP was observed in 8.5% of patients in the treatment group and 13% of patients in the control group. The Number needed to treat (NTT) was 20.<sup>[4]</sup> In the other meta-analysis, Lyu Y et al included a total of 21 RCTs. Their results have also shown that NSAIDs significantly reduce the incidence of PEP (p<0.00001).<sup>[5]</sup>

**Overall incidence**

The overall rate of PEP was higher in our study. PEP was observed in 17.8% (n=8/45) patients in the treatment group while it was diagnosed in 44.4% (n=20/45)

patients in the placebo arm ( $p=0.006$ ) on the other hand, in literature it varies from 2.1%-24.4%.<sup>[6]</sup> It shows us that PEP is more likely to occur in our setting.

#### Time of administration

Despite the ESGE (European Society of Gastrointestinal Endoscopy) guidelines recommendation that indomethacin or diclofenac may be administered rectally either before or after the endoscopic procedure, but theoretically the time of the administration can play a role in the prophylactic effectiveness.<sup>[7]</sup> The peak plasma concentration of diclofenac is reached 30 min after rectal administration.<sup>[8]</sup> Theoretically, therefore, rectal administration appears more reasonable before the ERCP than after it. In our study, the patients received the suppository 30 min before ERCP. It was illustrated in one of the meta-analyses that the administration of diclofenac pre-ERCP ( $p=0.001$ ) was more effective than post-ERCP use.<sup>[5]</sup> On the contrary, in other meta-analyses post-ERCP ( $p=0.0002$ ) appeared to be more effective in preventing PEP than indomethacin administration pre-ERCP ( $P=0.0003$ ).<sup>[4]</sup>

#### Route of administration

Many studies have been done to assess the most effective route of NSAIDs administration to prevent PEP. Most of the studies are done on the PR (Per-rectal) route. Some other studies comparing intramuscular, intravenous, and oral routes have also been conducted. We used the PR route as previous studies have demonstrated it to be the most effective. A recent trial by Ucar R, et al, aimed to evaluate the efficacy of intramuscular and rectal diclofenac sodium for prophylaxis of PEP found that the overall incidence of PEP was 6% ( $n=9$ ) and 2% ( $n=1$ ) in the intramuscular (IM) and rectal groups, respectively, and 14% in the control group ( $P=0.014$ ).<sup>[9]</sup>

Two meta-analyses have also supported this finding that PR diclofenac is the most effective route of administration. The first meta-analysis elaborated that only rectal administration reduced the incidence of PEP (6.8% vs. 13%;  $P<0.05$ ).<sup>[4]</sup> The other meta-analysis has also supported this finding that PEP decreased significantly only in patients receiving the drug rectally ( $p<0.00001$ ), but not for those who received intramuscularly ( $p=0.20$ ), intravenously ( $p=0.93$ ), and orally ( $p=0.62$ ).<sup>[5]</sup>

Another study has reinforced this finding that the incidence of PEP was significantly lower ( $p<0.001$ ) in the rectal diclofenac group with respect to other groups that tested oral, IV, or IM diclofenac.<sup>[10]</sup> But the sample size of this study was quite small, comprising only 20 subjects in each of the five groups.

#### Relationship of gender and PEP

In our study, PEP occurred more commonly in the male population, although it was statistically significant it is not compatible with the investigation conducted by another study that has shown that PEP occurred more

commonly in the female population.<sup>[11]</sup> Our research shows that sex can be related to the development of pancreatitis.

This study has a number of limitations. First, only patients with stones in CBD were selected, patients with leak, stricture, and cancer were not included in the study. Second, the data size consisted of 90 subjects only. A study with a large sample size would be required to detect a definite reduction in the occurrence of post-ERCP pancreatitis.

#### CONCLUSIONS

In summary, the present study is in favor of using rectal diclofenac to reduce the incidence of PEP. Considering the complications associated with PEP, rectal diclofenac is an easily available, safe, and inexpensive medication that can result in major clinical and economic benefits. We suggest further studies comparing combinations of treatment like the use of oral plus rectal diclofenac sodium compared with rectal alone in future studies.

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