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# Place of Rectal Indomethacin to Prevent Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Retrospective Study

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## Abstract

**Introduction:** Previous researches show that rectal indomethacin (RI) reduces the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). The aim of this study was to evaluate the utility of RI in preventing PEP.

**Methods**: We conceived a retrospective study including 89 patients who underwent ERCP at the Military Hospital Mohamed V of Rabat-Morocco over a period of 3 years (January 2019 to April 2022). We collected clinical features and procedures details from patients' records.

**Results**: A total of 89 patients were included for this study. PEP occurred in 12 of 89 (13,5%) patients. In the univariate analysis, the factors were associated with PEP are: administration of RI, pancreatic cannulation, difficult cannulation, number of pancreatic duct cannulation and the contrast injection into the pancreatic duct. In the multivariate analysis, when adjusting with other PEP risk factors, administration of RI and difficult cannulation were significantly associated with a higher risk of PEP. RI reduced the risk of PEP by 88% (OR 0.12, 95%CI 0.02 - 0.84, p = 0.03) and difficult cannulation increase the risk of PEP (OR = 3.97, 95%CI 0.71 - 0.84, p = 0.03).

**Conclusion:** Prophylactic rectal indomethacin significantly reduced the rates of PEP and should be administrated for all patients undergoing ERCP.

***Keywords:*** *Endoscopic Retrograde Cholangio-Pancreatography (ERCP); Rectal Indomethacin (RI); Pancreatitis (PEP)*

## Introduction

Endoscopic retrograde cholangio-pancreatography (ERCP) is a common procedure to diagnoses and treats diseases involving the bile duct and pancreas. However, ERCP is an invasive procedure that carries significant risks to the patient. Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common adverse that occurs with ERCP [1]. It occurs in 2% to 16% of patients in most studies. It can be a serious complication with the potential for significant morbidity and mortality [2-6].

Multiple risk factors for the development of PEP have been recognized. The risks most identified are female gender, younger age, smoking, suspected sphincter of Oddi dysfunction, prior PEP, difficult cannulation, contrast injection in pancreatic duct (PD) and pancreatic sphincterotomy [7,8].

Many approaches have been explored to reduce the risk of post-ERCP pancreatitis including the use of pharmacological agent. Thus, over than 35 drugs have been studied as prophylaxis against PEP. However, no medication has proved to be efficient to prevent post-ERCP pancreatitis with the exception of rectal non-steroidal anti-inflammatory drugs (NSAIDs). Rectal indomethacin (RI) used to manage the inflammation response that is presumed to be the development of PEP [9]. Two meta-analyses have demonstrated a significant benefit of RI indomethacin to prevent PEP [10,11]. Then, many guidelines used to recommend RI in all patients undergoing ERCP [12,13].

## Aim of the Study

Accordingly, the aim of our retrospective study was to evaluate the impact of RI in preventing PEP. Also, we identified the factors associated with the occurrence of PEP.

## Patients and Methods

This was a retrospective study including 89 patients underwent ERCP. Patients were enrolled from the gastroenterology I department Military Hospital Mohamed V of Rabat-Morocco over a period of 3 years (January 2019 to April 2022).

Clinical data were collected in all patients. All patients underwent ERCP at study entry. There were two groups: The indomethacin group consisted of patients who received 100 mg RI before or immediately after the ERCP and the second group consisted of patients who did not receive RI. PEP was defined by the presence of abdominal pain with a need for an extension of hospital stay or causing an unplanned admission coupled with an elevation of pancreatic enzymes three times the upper limit of the normal range 24 hours after the procedure.

The exclusion criteria were patients with kidney injury or current gastric ulcer.

### Statistical analysis

We used the Statistical Package for Social Sciences (SPSS) 20.0 to analyze the data. We tested continuous variables normality by the Kolmogorov-Smirnov test. All normally distributed data were expressed as mean ± standard deviation and the nonnormally distributed data were expressed as median and range. Comparison between two groups was done by Independent t-test. We used a multivariate logistic regression analysis model to evaluate predictors factors associated with PEP with its odds ratio and 95% confidence interval. A p value < 0.05 was considered statistically significant.

## Results

A total of 89 patients were included for this study. Demographic particulars and disease characteristics of patients are summarized in table 1.

| Variables | No rectal indomethacin group (n = 37) | Indomethacin group (N = 52) | P value |
|---|---|---|---|
| Age (years) | 60.2 ± 12.7 | 59.7± 15.1 | 0.86 |
| **Gender** | | | 0.14 |
| Males | 10 (27) | 22 (42.3) | |
| Females | 27 (73) | 30 (57.5) | |
| Smoking | 3 (8.1) | 9 (17.3) | 0.21 |
| Obesity (BMI>30) | 14 (37.8) | 10 19.2 | 0.05 |
| Antibioprophylaxis | 34 (91.9) | 49 (94.2) | 0.67 |
| History of ERCP | 9 (24.3) | 7 (13.5) | 0.19 |

| | | | |
|---|---|---|---|
| History of PEP | 1 (2.7) | 2 (3.8) | 0.77 |
| History of pancreatitis | 2 (5.4) | 4 (7.7) | 0.67 |
| Native papilla | 23 (62.2) | 36 (69.2) | 0.91 |
| **Indication** | | | |
| choledocholithiasis | 30 (81.1) | 39 (75) | |
| Pancreato-biliary malignancy | 7 (18.9) | 13 (25) | |
| **Procedural characteristics** | | | |
| Difficult cannulation | 14 (37.8) | 8 (15.4) | 0.02 |
| Pancreatic cannulation | 17 (45.9) | 16 (32.7) | 0.21 |
| Number of PD cannulation | 1.16 ± 1.6 | 0.81 ± 1.3 | 0.25 |
| Pancreatic duct injection | 6 (16.2) | 1 (1.9) | 0.01 |
| Biliary stent placement | 6 (16.8) | 9 (17.3) | 0.53 |
| Pancreatic stent placement | 3 (1.11) | 1(1.9) | 0.3 |
| Pancreatitis post ERCP | 10 (27) | 2 (3.8) | 0.001 |

***Table 1:*** *Clinical characteristics of patients who received rectal indomethacin with control group.*

*Data are presented as n (%) or mean ± standard deviation.Body Mass Index; ERCP: Endoscopic Retrograde Cholangiopancreatography; PEP: Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis.*

In general, PEP occurred in 12 of the 89 (13,5%) patients who underwent ERCP: 10 patients (27%) the RI group and 2 patients (3.8%) in the control group. The PEP rates were significantly higher compared to patients that received RI ($p < 0.001$).

A linear regression model was performed to elucidate the associations between previous variables and PEP. In the univariate analysis, the factors were associated with PEP are: administration of RI, pancreatic cannulation, difficult cannulation, number of PD cannulation and the contrast injection into the pancreatic duct (Table 2).

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI for OR | p-value | OR | 95% CI for OR | p-value |
| Administration of RI | 0.12 | 0.02 - 0.53 | <0.001 | 0.12 | 0.02-0.84 | 0.03 |
| Pancreatic cannulation | 11.04 | 2.24 - 24.3 | <0.001 | | | |
| Difficult cannulation | 3.97 | 1.075 - 14.76 | 0.04 | 3.97 | 0.71-22.11 | 0.04 |
| Number of PD cannulation | 2.13 | 1.41 - 3.21 | <0.001 | | | |
| Pancreatic duct injection | 33.75 | 4.91 - 232.26 | 0.03 | | | |

***Table 2:*** *Predictors factors of Post-endoscopic retrograde cholangiopancreatography pancreatitis.*

*OR: Odds Ratio; CI: Confidence Interval; RI: Rectal Indomethacin, PD: Pancreatic Duct.*

In the multivariate analysis, when adjusting with other PEP risk factors, administration of RI and difficult cannulation were significantly associated with a higher risk of PEP. RI reduced the risk of PEP by 88% (OR 0.12, 95%CI 0.02-0.84, $p = 0.03$) and difficult cannulation increase the risk of PEP (OR = 3.97, 95%CI 0.71-0.84; $P = 0.03$) (Table 2).

## Discussion

Our results showed that rectal indomethacin administration given before and after ERCP decreased significantly the incidence of post-ERCP pancreatitis ($p < 0.001$).

The first randomized controlled trial was conducted by Murray., *et al*. that established the efficacy of rectal diclofenac administration after ERCP to prevent PEP. The incidence of PEP was reduced in the diclofenac group when compared to control group (6.4% vs. 15.5%, p = 0.049) [14].

Then, many trials evaluate the role of NSAID's especially indomethacin to prevent PEP. In a meta-analysis of four studies including a total of 912 patients who received RI, the results showed a relative risk for PEP of 0.36 (95%CI 0.22 - 0.60) after administration of prophylactic NSAIDs [15].

Various mechanisms are involved in the pathophysiology of PEP. This events lead to a inappropriate activation of pancreatic enzymes and auto-digestion. The main mechanisms by which NSAIDs act is the inhibition of cyclooxygenase (COX). COX2 is the enzyme that catalyzes the conversion of arachidonic acid to prostaglandin and thromboxane which are known to be implicated in acute inflammatory process during acute pancreatitis [16].

Another meta-analysis concerning 6 randomized controlled trials that include 1300 patients revealed a statistically significantly lower risk of PEP in the NSAIDs group in comparison to control group [17].

Our data show differences in clinicals characteristics and procedural risk factor between the 2 groups. We notice in indomethacin group a high proportion of history of pancreatitis (7.7% vs 5.4%, p = 0.19) and native papilla (69.2% vs 62,2%, p = 0.91) when compared to the control group. In the otherwise, the control group had a higher prevalence of procedural risk factors: pancreatic duct cannulation (45.9% vs 32.7%, p = 0.01), difficult cannulation (37.8% vs 15.4%, p = 0.02), pancreatic duct injection (16.2% vs 1.9%, p = 0.01).

Identification of risk factors is important to the selection of high-risk patients in which prophylaxis endoscopic or pharmacologic measures should be considered during ERCP. In our study, we demonstrate that pancreatic duct injection, difficult cannulation and pancreatic cannulation were associated with PEP. This goes in line with previous studies conducted by Freeman and Al [4]. It showed that difficult cannulation was significantly associated with risk of PEP. Pancreatitis occurred in 12.5% (35 of 279) of patients in whom cannulation was difficult (OR 3.4). Also, pancreatic duct injection was significantly associated with risk of pancreatitis (OR 3.1). PEP occurred in 7.1% to 11% of patients, this depend of the number of PD injections [4].

## Limitation of the Study

This study has some limitations. Our study is retrospective and was conducted among in patients at our department. Therefore, our findings cannot be representative of the general population. A multicentric cohort with a larger sample size will help to better estimate the place of rectal indomethacin in prophylaxis of PEP.

## Conclusion

In conclusion, this present study has demonstrated that prophylactic rectal indomethacin significantly reduced the rates of PEP. Given the safety and the low price to RI, it may be administrated for every patient undergoing ERCP.

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