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Research Article

**EFFICACY OF RECTAL INDOMETHACIN IN PREVENTION
OF POST-ERCP PANCREATITIS****Dr. Hina Fatima¹, Dr. Rabbia Farooq², Dr. Ziyad Humayun Akhtar³, Dr. Ikram Ul Haq Raja⁴,
Dr. Bushra Ali⁵, Dr. Arif Amir Nawaz⁶**¹ Demonstrator Anatomy department Fatima Memorial Medical and Dental College, Lahore² Sheikh Zayed Medical College/Hospital, Rahim Yar Khan³ Medical Officer, Hayat Memorial Hospital, Lahore⁴ Resident Gastroenterology Department, Fatima Memorial Hospital, Lahore⁵ Assist prof. Gastroenterology Department, Fatima Memorial Medical and Dental College, Lahore⁶ Prof. Gastroenterology Department, Fatima Memorial Medical and Dental College, Lahore**Abstract:**

Background: Acute pancreatitis is a common and serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) accounts for substantial annual morbidity and health care expenditure, and occasional death. The prevention of PEP is an ongoing area of active research. Several proposed pharmacologic agents and therapeutic techniques have been proposed to reduce the risk of PEP. Nonsteroidal antiinflammatory drugs (NSAIDs) reduce incidence of PEP in both high- and low-risk patients. Rectal NSAIDs are among the few agents shown to be effective in preventing PEP. Indomethacin is one of the NSAIDs used in the clinical trials. The objective of this study was to compare the frequency of Post ERCP Pancreatitis in patients treated with or without rectal indomethacin.

Methodology: A prospective, randomized controlled study conducted in tertiary care hospital on 300 patients randomized to receive a suppository containing 100 mg indomethacin or no suppositories, just after completion of ERCP. Post-ERCP pancreatitis was evaluated by amylase and lipase levels in patients with epigastric pain, 4 hours after ERCP. **Results:** In our study, mean age was recorded as 56.28±8.39 in Indomethacin and 55.72±7.84 years in those without Indomethacin group, 55.33%(n=83) in Indomethacin and 53.33%(n=80) in those without Indomethacin group were male while 44.67%(n=67) in Indomethacin and 46.67%(n=70) in those without Indomethacin group were females. Comparison of frequency of Post ERCP Pancreatitis in patients treated with or without rectal indomethacin was done, it shows that 5.33% (n=8) in Indomethacin and 12.67% (n=19) in those without Indomethacin group, p value was calculated as 0.02 showing a significant difference between the two groups. **Conclusion:** We concluded that the frequency of Post ERCP Pancreatitis is significantly lower in patients treated with rectal indomethacin when compared to those without it.

Keywords: Post ERCP Pancreatitis, rectal indomethacin.

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INTRODUCTION:

Endoscopic Retrograde Pancreaticholangiography (ERCP) is one of the most commonly performed, most complex and high risk endoscopic procedure performed for the treatment of various conditions of biliary and pancreatic ductal system [1]. ERCP has a higher potential for complications that range from mild, non-lethal incidents with immediate resolution to major life threatening crises [2,3]. A feared complication of ERCP is post-ERCP Pancreatitis (PEP) which occurs in 30 to 40 % of high risk patients [4,5].

PEP is defined as new or worsened abdominal pain and serum amylase level 3 times or more above the upper limit of normal, measured after 24 hours of the procedure [6]. PEP is graded as mild, moderate and severe depending on length of hospital stay & complications of the procedure. [7]. The incidence of the PEP is approximately 5 to 10% [8]. The prevalence of PEP ranges from 1.3 to 8%.¹ The mortality rate of PEP is about 0.1 to 0.5%.⁹ The pathophysiology of PEP includes various initiating events that lead to activation of pancreatic enzymes & auto digestion [10]. PEP causes mechanical, chemical, hydrostatic, enzymatic, microbiologic, allergic or thermal disruption [11]. Multiple risk factors for the PEP have been identified and are broadly categorized into operator dependent, patient dependent & procedure dependent factor [3,12].

PEP appears unavoidable even in the hands of expert endoscopist. As a result, numerous endoscopic & pharmacologic interventions have been attempted to reduce the rate of complications [7]. Interventions include pancreatic duct (PD) stent placement, prophylactic placement of pancreatic duct wire guided cannulation, early precut biliary sphincterotomy and fistulotomy [8]. Pharmacologic prophylaxis of PEP includes the administration of nifedipine, nitrates, heparin, allopurinol, N-acetylcystine, NSAIDs and many others. Majority of these agents showed disappointing results for prevention of PEP.⁹ So prophylactic placement of PD stent has gained widespread acceptance [10].

Rectal NSAIDs are among the few agents shown to be effective in preventing PEP [15]. Indomethacin is one of the NSAIDs used in the clinical trials. It may be administered rectally either before or after the procedure. NSAIDs act by inhibition of cyclooxygenase (COX), inhibition of phospholipase A2 (PLA), prevention of leukocyte adhesion and migration, and inhibition of integrin [16-19]. Initially studies were done to evaluate the role of oral, I/M NSAIDs, Ebbelohj N *et al* used rectal suppositories to

demonstrate the effect on frequency & intensity of pancreatitis [20]. Rectal indomethacin has become a potential candidate as an ideal pharmacologic agent for preventing PEP. They may obviate the need for prophylactic pancreatic stent placement. Rectal Indomethacin like other NSAIDs is more attractive to use because of convenience, safety, cost effectiveness, ease of administration & known favorable profile [21-24].

In May 2014, Imran Sheikh *et al* reported that PEP was reduced in the NSAID group compared to those receiving Placebo (6.4% Vs 15.5%, P= 0.049) [6] while in August 2014, Zoltan Dobronte *et al* reported that there was no significant difference between indomethacin and placebo groups in the incidence of PEP (5.8 Vs 6.9) [5].

Multiple studies have been conducted internationally regarding the efficacy of indomethacin in preventing PEP but the research work is lacking at national level so I want to conduct research in our population. Different studies have shown contradictory results regarding the use of indomethacin. The objective of this study is to know effectiveness of rectal indomethacin as it can be the best alternative to PD stent which is expensive, invasive and with multiple complications.

METHODOLOGY:

This randomized control study was conducted at Gastroenterology department, Fatima Memorial Hospital, Lahore. 300 (150 in each group) patients were included in the study who underwent ERCP from Jan 2016 to March 2017. Patients divided into two groups. One group (150 patients) was given per rectal indomethacin (2 suppositories 50 mg each) while other group (150 patients) given no suppositories. Patients already had raised amylase or acute pancreatitis, history of chronic pancreatitis or had a contraindication to NSAIDs were excluded from the study. An informed consent was obtained from eligible patients before the start of procedure and preliminary enrolment was performed. Approval of the study was taken from hospital ethical review board. ERCP was done under monitored anesthesia care (MAC).

Patients were randomly assigned by lottery method to receive either two 50mg indomethacin suppositories or no suppositories. The suppositories were administered immediately after ERCP while the patient was still in procedure room. Patients were monitored in the recovery area for epigastric pain. Serum amylase and lipase were obtained in symptomatic patients. Symptomatic patients were

kept under observation for further 2 to 3 days, if already not admitted in the hospital. All patients were discharged after 4 hours, if there were no complications. Serum amylase and lipase level were seen in all symptomatic patients at 4 hours and at 24 hours. The diagnosis of PEP was made on the presence of typical pain and a rise in amylase and lipase more than three times upper limit of normal. Patients developing PEP were managed conservatively by admitting the patient in hospital and giving I.V fluids and I.V analgesics.

The data was entered and analyzed by SPSS version 20. Mean and standard deviation (SD) was calculated from quantitative variables e.g. age, pancreatic enzyme. Frequency & percentage was calculated for qualitative variables e.g. gender and PEP. The data was stratified for age, gender. Chi square test was applied to know the significance. Data was stratified for age, gender and diagnosis to deal with effect modifiers. Post stratification chi square test was applied taking p value as ≤ 0.05 as significant.

RESULTS:

A total of 300 cases (150 in each group) fulfilling the inclusion/exclusion criteria were enrolled to compare

the frequency of Post ERCP Pancreatitis in patients treated with or without rectal indomethacin. Age distribution of the patients was done, it shows that 30%(n=45) in Indomethacin and 29.33%(n=44) without Indomethacin group were between 15-50 years of age while 70%(n=105) in Indomethacin and 70.67%(n=106) without Indomethacin group were between 51-85 years of age, mean \pm sd was calculated as 56.28 \pm 8.39 and 55.72 \pm 7.84 years in both groups respectively. (Table No. 1) Gender distribution shows that 55.33 %(n=83) in Indomethacin and 53.33%(n=80) in those without Indomethacin group were male while 44.67%(n=67) in Indomethacin and 46.67%(n=70) in those without Indomethacin group were females. (Table No. 2)

Comparison of frequency of Post ERCP Pancreatitis in patients treated with or without rectal indomethacin was done, it shows that 5.33%(n=8) in Indomethacin and 12.67%(n=19) in those without Indomethacin group while 94.67%(n=142) in Indomethacin and 87.33%(n=131) in those without Indomethacin group had no PEP, p value was calculated as 0.02 showing a significant difference between the two groups. (Table No. 3)

TABLE No. 1
AGE DISTRIBUTION (n=300)

Age (in years)	Indomethacin (n=150)		Without Indomethacin (n=150)	
	No. of patients	%	No. of patients	%
15-50	45	30	44	29.33
51-85	105	70	106	70.67
Total	150	100	150	100
Mean\pmSD	56.28\pm8.39		55.72\pm7.84	

TABLE No. 2
GENDER DISTRIBUTION (n=300)

Gender	Indomethacin (n=150)		Without Indomethacin (n=150)	
	No. of patients	%	No. of patients	%
Male	83	55.33	80	53.33
Female	67	44.67	70	46.67
Total	150	100	150	100

TABLE No. 3
COMPARISON OF FREQUENCY OF POST ERCP PANCREATITIS IN PATIENTS TREATED WITH OR WITHOUT RECTAL INDOMETHACIN (n=300)

PEP	Indomethacin (n=150)		Without Indomethacin (n=150)	
	No. of patients	%	No. of patients	%
Yes	8	5.33	19	12.67
No	142	94.67	131	87.33
Total	150	100	150	100

DISCUSSION:

Acute pancreatitis is a common and serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) account for substantial annual morbidity and health care expenditure, and occasional death.^{25, 26} Prevention of PEP is an ongoing area of active research. Several proposed pharmacologic agents and therapeutic techniques have been proposed to reduce the risk of PEP. Nonsteroidal antiinflammatory drugs (NSAIDs) reduce incidence of PEP in both high- and low-risk patients. Rectal NSAIDs are among the few agents shown to be effective in preventing PEP.¹³ Indomethacin is one of the NSAIDs used in the clinical trials.

The current study was planned with the view that multiple studies have been conducted internationally regarding the efficacy of indomethacin in preventing PEP but the research work is lacking at national level so we planned this research in our population. Different studies have shown contradictory results regarding the use of indomethacin. We wanted to know its effectiveness as it can be the best alternative to PD stent which is expensive, invasive and with multiple complications.

In our study, mean age was recorded as 56.28 ± 8.39 in Indomethacin and 55.72 ± 7.84 years in those without Indomethacin group, 55.33% (n=83) in Indomethacin and 53.33% (n=80) in those without Indomethacin group were male while 44.67% (n=67) in Indomethacin and 46.67% (n=70) in those without Indomethacin group were females. Comparison of frequency of Post ERCP Pancreatitis in patients treated with or without rectal indomethacin was done, it shows that 5.33% (n=8) in Indomethacin and 12.67% (n=19) in those without Indomethacin group while 94.67% (n=142) in Indomethacin and 87.33% (n=131) in those without Indomethacin group had no PEP, p value was calculated as 0.02 showing

a significant difference between the two groups.

Our findings are in agreement with a study conducted in May 2014 by Imran Sheikh et al who reported that PEP was reduced in the NSAID group compared to those receiving Placebo (6.4% Vs. 15.5%, $P = 0.049$) [10] Our findings were also consistent in regards of effectiveness of NSAIDs in prevention of PEP as shown in the studies including Murray et al [21] (6.3 vs. 15%), Sotoudehmanesh et al [22] (3.2 vs. 6.8%) Khoshbaten et al²³ (4 vs. 26%) while in August 2014,

Zoltan Dobronte et al reported that there was no significant difference between indomethacin and placebo groups in the incidence of PEP (5.8 Vs 6.9).⁹ the findings of our study are not consistent with this study.

B. Joseph Elmunzer and others [13] in a multicenter, randomized control trial suggested that rectally administered nonsteroidal antiinflammatory drugs may reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). They recorded that out of total of 602 patients, the majority of patients (82%) had a clinical suspicion of sphincter of Oddi dysfunction. Post-ERCP pancreatitis developed in 27 of 295 patients (9.2%) in the indomethacin group and in 52 of 307 patients (16.9%) in the placebo group ($P = 0.005$). Moderate-to-severe pancreatitis developed in 13 patients (4.4%) in the indomethacin group and in 27 patients (8.8%) in the placebo group ($P = 0.03$).

Another study¹⁴ investigated and compared 2 clinical strategies to prevent postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and recorded that out of 623 patients with high-risk factors, 145 pairs were generated after propensity score matching. Thirty-two patients developed pancreatitis—10 (6.9 %) in the pancreatic stent placement (PSP) group and 22 (15.2 %) in the rectal indomethacin group ($P = 0.025$). Moderate-to-severe

pancreatitis developed in 5 patients (2.8%) in the pancreatic stent placement group and 14 patients (9.7%) in the rectal indomethacin group ($P=0.047$). They were of the view that although indomethacin represents an easy, inexpensive treatment, prophylactic PSP is still the better prevention strategy for PEP. In summary, the results of our study in agreement with other above mentioned studies justify that there is a difference in frequency of Post ERCP Pancreatitis in patients with administration of rectal indomethacin and without administration of rectal indomethacin.

CONCLUSION:

We concluded that the frequency of Post ERCP Pancreatitis is significantly lower in patients treated with rectal indomethacin when compared to those without it.

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