PROPHYLACTIC RECTAL NSAIDS IN THE PREVENTION OF POST-ERCP PANCREATITIS

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ABSTRACT

Objective: To evaluate the effectiveness of rectal non-steroidal anti-inflammatory drugs (NSAIDs) using diclofenac in preventing pancreatitis following ERCP.

Methodology: It was a randomized, double blinded, placebo controlled study carried out at Surgical Unit-I, Holy Family Hospital, Rawalpindi from May 2013 to April 2014. A total of 108 patients were included and randomly assigned in each of study and placebo groups. Group I patients received 100 mg of diclofenac per rectally while group II patients received a glycerine suppository per rectally (placebo) before the start of ERCP. Post ERCP pancreatitis (PEP) was diagnosed by clinical evaluation and raised serum amylase levels after four hours of the procedure in both groups (study vs control).

Results: Out of 108 patients 32 were males and 76 were females. Mean age was 46.09 ±12.31 in group I, while it was 42.93 ±14.69 in Group II. Mean serum amylase level, 4 hours after ERCP, was 184.70 ±36.34 in the diclofenac group, while it was 388.20 ±57.27 IU/L in the control group. Thirty one patients were diagnosed with Post ERCP pancreatitis, out of which nine patients belonged to the study group and twenty two were of the control group (P = 0.000).

Conclusion: Per-rectal administration of diclofenac suppository prior to ERCP results in significant reduction in the frequency of ERCP induced pancreatitis.

Key Words: Pancreatitis, Diclofenac, Endoscopic retrograde cholangiopancreatography, Nonsteroidal anti-inflammatory drugs

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography is a useful diagnostic and therapeutic tool in pancreato-hepatobiliary diseases[1]. ERCP induced pancreatitis is the most common complication, with a frequency ranging from 1 to 40 percent[2].

Pancreatitis is known for increased healthcare expenses, significant morbidity and unusual mortality[3]. Pancreatic duct imaging with/without instrumentation leads to an acute inflammatory process which is supposed to be an important factor in the pathogenesis of post ERCP pancreatitis. Phospholipase A2 is considered to be a significant factor in the initiation of inflammatory cascade of pancreatitis[4]. The initial injury results in premature activation of proteolytic enzymes, auto digestion, and abnormal acinar secretion, which leads to systemic and local manifestation of pancreatitis[5].

Pharmacological prophylaxis of pancreatitis after PEP has remained the subject of various trials in recent years. However, high quality clinical trials failed to provide an effective pharmacologic prophylaxis for ERCP induced pancreatitis[3]. Despite these disappointing results, pharmacoprevention of PEP remains an area of active research.

NSAIDs have shown the most encouraging results in this respect, by attenuating the inflammatory response seen in pancreatitis[6]. An NSAID like diclofenac, inhibits phospholipase A2[7]. It hinders neutrophil/ endothelial cell attachment, thereby restricting the accumulation of neutrophils at the site of tissue injury. In addition, these also prevent the expression of nitric oxide synthase, which is linked with inflammation and cell damage[4].

Nonsteroidal anti-inflammatory drugs are favoured for being economical, convenient to use, and safe[8]. Prospective clinical trials have shown that NSAIDs induced adverse events, such as post-ERCP hemorrhage, is comparable in the NSAIDs and placebo groups[6]. Therefore, routine use of NSAIDs leads to decreased incidence of PEP. This ensures important clinical and economic benefits[9]. Khoshbaten M et al showed that post ERCP pancreatitis developed in 4% of patients in the diclofenac

group as compared to 26% in the placebo group (P< 0.01)[6].

At present, a wide variety of literature exists on the pharmacologic prevention of ERCP induced pancreatitis. Debate is still going on, within the literature, on the use of best pharmacologic agent, timing and route of administration. Unfortunately, no local data is available. The aim of our study was to determine whether rectal administration of diclofenac at the dose provided can effectively prevent ERCP induced pancreatitis. This is proposed as a valuable and simple method of avoiding a deadly complication of ERCP and be easily incorporated in our management plan. Prevention of PEP would lead to a considerable decline in morbidity and mortality rates.

METHODOLOGY

A randomized, double blinded, placebo controlled study was conducted at Surgical Unit-I, Holy Family Hospital, Rawalpindi from May, 2013 to April, 2014. Institutional Research Ethical Committee gave the approval for this study. All patients were kept blinded to the group allocated throughout the study.

One hundred and eight (108) patients, who met inclusion criteria, were scheduled for ERCP. Informed written consent was signed by all patient. Patients were considered eligible if they met the inclusion criteria: patients undergoing ERCP on an elective basis due to deranged liver function tests and/or extrahepatic cholestasis, both gender, and age between 18 & 80 years. Exclusion criteria included patients who had chronic pancreatitis, developed acute pancreatitis 2 weeks prior to ERCP or if the procedure was done for biliary stent removal or exchange. All those patients who had history of peptic ulcer disease & chronic renal failure, hypersensitivity to NSAIDs, and those who consumed an NSAID in the previous week were also omitted.

Each individual was randomly assigned to one of two groups by lottery method. The envelope was opened in the procedure room by the assisting nursing staff prior to induction of anesthesia for ERCP to indicate which patient is to receive per rectal 100 mg diclofenac suppository (Group I) or per rectal glycerine suppository (Group II, placebo). 54 patients received per rectal diclofenac suppository 100 mg (Group I), and 54 patients received per rectal glycerine suppository (Group II).

Patients were sedated with intravenous midazolam. Xylocaine spray provided local anesthesia in the oral cavity. In both the groups, ERCP was performed by the consultant endoscopist. The diclofenac suppositories were purchased from a single vendor.

At the end of ERCP, the endoscopist documented its procedural elements, along with the type of cannulation and therapeutic biliary sphincterotomy, if performed. Patients were observed in post anesthesia care unit (PACU) by resident surgeon for four hours after ERCP. All patients were clinically evaluated at 4 hours post ERCP and serum amylase levels sent at the same time. Patient demographics, risk factors, details of the procedure and any untoward event was recorded on a specially designed performa. All the possible confounding variables were taken into consideration & bias removed by randomization.

Post-ERCP pancreatitis was the primary outcome. Any patient developing epigastric pain with guarding and/or vomiting, an elevated pancreatic enzyme (serum amylase) levels with greater than four-fold the upper limit of normal (>400 IU/L), was diagnosed with post-ERCP pancreatitis.

SPSS software (SPSS Version 16) was used for data analysis. Descriptive statistics were calculated for both qualitative and quantitative variables. Gender and pancreatitis were expressed as frequencies & percentages. Mean ± SD was calculated for age and serum amylase levels. Chi square test was employed to analyze the frequency of pancreatitis between the two study groups. Qualitative variables were presented through tables and figure. P value of <0.05 was considered statistically significant.

RESULTS

Out of 108 patients, 32 were males and 76 were females. The study population was in age group of 21 to 74 years (mean age 44.51 ±13.58 years). Mean age was 46.09 ±12.31 in group I, while it was 42.93 ±14.69 in Group II. Demographic characteristics and procedural elements of ERCP are listed in Table 1.

Four hours following ERCP, mean amylase level was 184.70 ± 36.34 IU/L in the study group and 388.20 ±

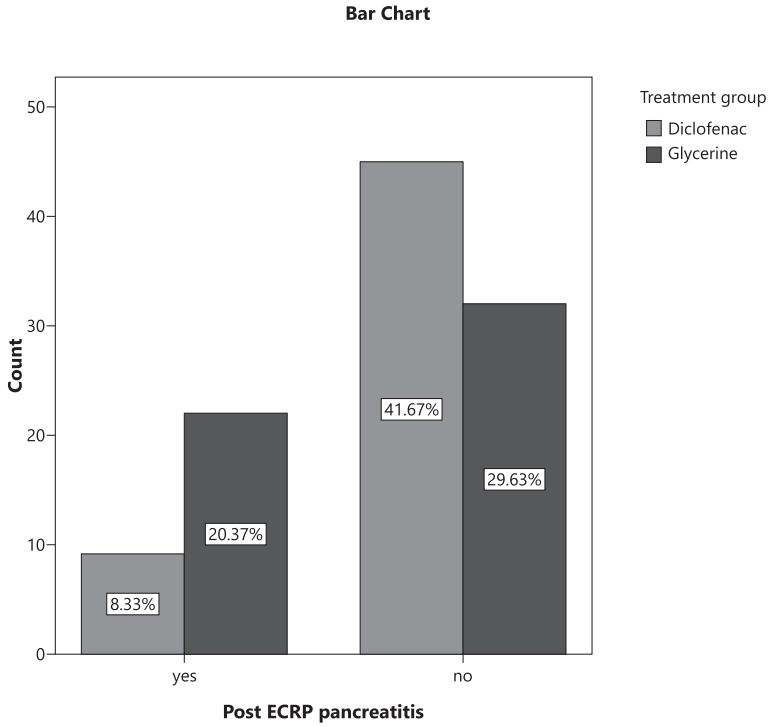
Table 1: Patient characteristics

Post ERCP amylase at 4 hours		
Characteristics	**Diclofenac (n=54)**	**Glycerine (n=54)**
Age (years)	46.09±12.31	42.93±14.69
Female sex — No. (%)	41 (75.92%)	35 (64.81%)
Difficult cannulation— No. (%)	12 (22.22%)	13 (24.07%)
Therapeutic biliary sphincterotomy — No. (%)	25 (46.30%)	35 (64.81%)

Table 2: Serum amylase levels 4 hours post ERCP in both groups

Post ERCP amylase at 4 hours				
Treatment Group	**n**	**Mean**	**Std. Deviation**	**P Value**
Diclofenac	54	184.70	267.026	0.001
Glycerine	54	388.20	420.878	

Figure 1: Post ERCP Pancreatitis in both groups



57.27 IU/L in the placebo group (Table 2). This difference in mean values of amylase levels was statistically significant (P = 0.001). ERCP induced pancreatitis developed in 31 patients (28.70%); 9 were of the diclofenac suppository group and 22 patients from the control group (Figure 1). All patients were discharged without any adverse event in the post procedure period. No severe side-effects were noted with a single dose of NSAID (diclofenac).

DISCUSSION

Pancreatitis is a frequent and grave complication of endoscopic retrograde cholangiopancreatography (ERCP)[10]. So far, many speculations exist regarding the underlying mechanisms of post ERCP pancreatitis. Any traumatic or thermal injury to papilla initiates a cascade of acute inflammatory process resulting in spasm or edema of sphincter of oddi, thereby transiently obstructing the pancreatic duct[6]. This leads to intra-pancreatic ductal hypertension and acinar damage, ultimately resulting in pancreatitis. A delay of approximately 4.5 hours exists between pancreatic insult during ERCP and appearance of clinical features of pancreatitis[11]. Anti-inflammatory mechanisms can be employed in this 'therapeutic window' to modulate the inflammatory response. The role of NSAIDs in inhibiting the synthesis of prostaglandins is well established in literature. When tested in vitro, this class of drugs is known to have a potent inhibitory effect on Phospholipase A2 activity in post ERCP patients. There is documented evidence that NSAIDs inhibits neutrophil/ endothelial cell attachment, thereby restricting the accumulation of neutrophils at the site of tissue injury. In addition, these also prevent the expression of nitric oxide synthase, which is linked with inflammation and cell damage[6].

It is essential to differentiate between hyperamylasemia and pancreatitis seen after ERCP. Elevated serum amylase levels is known as hyperamylasemia. More than 75% patients undergoing ERCP present with hyperamylasemia without any clinical evidence of acute pancreatitis[12].

Our study showed that a single diclofenac suppository (100 mg) administered at the time of induction for ERCP, can reduce the incidence of a common but serious complication i.e., post-ERCP pancreatitis. The severity of PEP was not linked to the administration of diclofenac suppository, as confirmed by different published meta-analysis[4,13,14].

NSAID related decline in the incidence of PEP was not observed in the trial of Cheon et al[15]. The reason for a negative association between NSAIDs and decreased incidence of PEP is possibly linked to the fact that gastric acid may cause destruction of orally administered NSAIDs; moreover reduced bioavailability is attributed to extensive first-pass metabolism. Such factors may cause inactivation of NSAIDs, ultimately leading to an insignificant reduction of PEP. It takes 30 to 90 minutes for a rectally administered diclofenac suppository to reach its peak concentrations, with complete bioavailability. Plasma half-life is approximately 2 hours; however after 3-4 hours of administration, 90% of the drug is excreted from the body[6].

In the present study, the frequency of ERCP induced pancreatitis was 29%, with a significant P-value (P=0.000) between the two study groups (41% in glycerine suppository group vs 16% in diclofenac group). We observed a much greater frequency of PEP in the control group, as compared to the results of previously published literature (18.8%[16] and 16.9%[3]).

68% of the patients included in our study had common bile duct stones. This finding defines a high risk group of patients for developing ERCP induced pancreatitis. Our results are comparable with other published data, with similar patient groups being surveyed (11.3[17], 15%[18], 18%[19] and 24%[20]).

Prospective studies on established risk factors for post ERCP pancreatitis showed no considerable distinction between the two study groups. These findings concur with those of Elmunzer et al[3].

We conclude that prophylactic administration of rectal NSAIDs (diclofenac) in patients undergoing ERCP is safe, feasible, and effective with negligible side effects. This method of prophylaxis is cost-effective and productive treatment modality, especially in resource strained hospitals. However, lack of evidence and supporting data precludes the use of NSAIDs in this respect.

The main limitation of our study was the lack of pain estimation, using a standard pain scale. Only the presence or absence of epigastric pain following ERCP was recorded, making it a challenging task to compare it with other published literature. Moreover, epigastric pain and hyperamylasemia were the only criterion used for establishing a diagnosis of PEP. This leads to, some degree of, uncertainty in calculating the accurate frequency of post-ERCP pancreatitis between the two study groups. however, several previous studies used the same criteria for diagnosing PEP[21,22]. We recommend the use of additional modalities (e.g. contrast enhanced computed tomography and/or ultrasonography) for a more promising diagnosis.

CONCLUSION

Per-rectal administration of diclofenac suppository prior to ERCP results in significant reduction in the frequency of ERCP induced pancreatitis.

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CONTRIBUTORS

MSS conceived the idea, reviewed the literature, analyzed the data and drafted the manuscript. MUF helped in manuscript writing. SZ helped in data management. MN and RA helped in literature review. JSK supervised the study and gave final approval of the article. All authors contributed significantly to the submitted manuscript.