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Role of rectal diclofenac suppository for prevention and its impact on severity of post-ERCP pancreatitis in high risk patients

Sandeep Patil, Vikas Pandey, Nilesh Pandav, Meghraj Ingle, Aniruddha Phadke, Prabha Sawant

ABSTRACT

Aims: To study the role of rectal diclofenac in prevention of post-ERCP (endoscopic retrograde cholangiopancreatography) pancreatitis and its impact on severity of post-ERCP pancreatitis. Methods: We conducted a single centre, prospective, open labelled, randomized trial for evaluating the use of rectal diclofenac in prevention of post-ERCP pancreatitis in high risk patients. We assessed 526 patients given for ERCP for different indications. 400 patients were eligible for the study. Those not fitting the high risk criteria and with acute pancreatitis were excluded. These patients were randomized in two groups, 200 patients received rectal diclofenac prior to or during the procedure while 200 patients received placebos. Serum amylase was measured at 2 hr and 36 hr. Post-ERCP pancreatitis was defined as serum amylase > 3 times ULN associated with severe abdominal pain. Severity was graded according to days of hospitalization and complications. Results: 29 out of 400 (7.2%) patients developed post-ERCP pancreatitis. 6 out of 200 (3%) patients in rectal diclofenac group developed post-ERCP pancreatitis compared to 23 out of 200 (11.5%) patients in placebo group. The difference was statistically significant (p=0.001). All patients (6) in rectal diclofenac group developed mild pancreatitis as compared to severe pancreatitis in four and moderate pancreatitis in five patients in the placebo group. Conclusion: Rectal diclofenac prior to or during ERCP in high risk patient reduces the incidence as well as severity of post-ERCP pancreatitis compared to placebo.

Keywords: Post-ERCP pancreatitis, Rectal diclofenac, Sphincter of Oddi dysfunction

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INTRODUCTION

Pancreatitis is a major well known complication of endoscopic retrograde cholangiopancreatography

(ERCP) with reported incidence ranging from 1–10% in various series [1–3]. It can cause significant morbidity and occasional deaths are also reported. The risk factors for post-ERCP pancreatitis are well known [4]. Various theories about pathogenesis of post-ERCP pancreatitis have been proposed. But the most accepted theory is mechanical trauma to papilla or pancreatic sphincter causing transient obstruction to outflow of pancreatic juice. Another theory suggests the increased hydrostatic pressure in pancreatic duct caused by injection of contrast or saline cause injury to parenchyma. Regardless of mechanism, the cascade of events is initiated resulting in activation of proteolytic enzymes causing autodigestion of pancreas and impaired acinar secretion. This results in activation of inflammatory cascade causing both local inflammation and systemic effects [5, 6]. The interventions for prevention of post-ERCP pancreatitis aim at breaking this cascade. Nonsteroidal anti-inflammatory drugs are potent inhibitor of phospholipase A2 which is thought to play a critical role in early inflammatory cascade [7]. Rectal diclofenac is a cheap, widely available agent with easy method of administration and favorable side effect profile makes it a attractive option. There is limited data on efficacy of NSAIDS in prevention of post-ERCP pancreatitis. Rectal diclofenac have been evaluated in few trials earlier but most trials included low risk patients and sample size of these trials was very small. Till date no Indian studies are available to the best of our knowledge which evaluated rectal diclofenac in prevention of post-ERCP pancreatitis. We conducted a prospective, single centre, open labeled, randomized placebo controlled trial evaluating role of rectal diclofenac in prevention of post-ERCP pancreatitis in high risk patients and whether it has any implications on severity of post-ERCP pancreatitis.

MATERIALS AND METHODS

This study was performed at a tertiary care centre between August 2011 and June 2014. We enrolled 526 patients that were referred for ERCP for different indications [flowchart 1]. Inclusion criteria involved only those patients with high risk for developing post-ERCP pancreatitis. Patients were considered having high risk of development of post-ERCP pancreatitis if they had one or more major risk factors: suspected sphincter of Oddi dysfunction, prior history of post-ERCP pancreatitis, difficult or failed cannulation (more than five attempts), repeated pancreatic cannulation, pancreatic duct injection with acinarisation, pancreatic sphincterotomy, precut sphincterotomy, biliary sphincterotomy for suspected SOD, ampullectomy; or if they had two or more minor risk factors for development of post-ERCP pancreatitis: female gender, young age, history of recurrent acute pancreatitis, normal serum bilirubin, lack of choledocholithiasis, pancreatic brush cytology, balloon dilatation of intact biliary sphincter. Those patients (i) who did not fit the high risk criteria, (ii) had acute pancreatitis at the time of ERCP, (iii) had contraindications to the use of NSAIDs (active peptic ulcer disease or serum creatinine > 1.4 mg/dl), and (iv) who had ingested NSAIDs in last 1 week, were excluded from the study. 400 patients were eligible for the study. Total 126 patients were excluded from the study depending on the exclusion criteria. These patients were randomized in two groups each containing 200 patients. Randomization was done in 1:1 ratio by computer generated method. It was balanced in random blocks of five patients. One group (n=200) received rectal diclofenac suppository (containing 100 mg of diclofenac) immediately prior to the procedure. Other groups (n=200) received glycerin suppositories as placebos. The ERCP was performed under sedation with intravenous midazolam by two experienced operators. Injection hyoscine was given for control of bowel motility. During the procedure an assistant recorded the details of the procedure viz timing of procedure, number of pancreatic duct cannulation and injection, difficulty in cannulation, whether precut, pancreatic sphincterotomy, balloon sphincteroplasty was done. Patients in rectal diclofenac or placebo group received rectal suppository immediately prior to or during the procedure. Pancreatic duct stents were placed in those patients in which pancreatic cannulation occurred more than two times or pancreatic injection with contrast or saline occurred during the procedure. Maximum procedure time for the ERCP was 70 min. Post procedure patients were admitted for observation. Patients were assessed for any immediate complications, such as abdominal pain or distension. Patients were subjected to testing of serum amylase at 2 hr and 36 hr post procedure. Those patients who had no abdominal pain, vomiting, back pain and 2 hr serum amylase levels less than 2 times upper limit of normal were started on oral liquids 3–4 hours after ERCP. Post-ERCP pancreatitis was defined as rise in serum amylase more than three times upper limit of normal 24 hours after ERCP with associated clinical feature of severe abdominal pain requiring persistent hospitalization. Primary end point of the study was to detect number of patients developing post-ERCP pancreatitis in both the groups. Those patients diagnosed as post-ERCP pancreatitis were kept hospitalized. These patients received intravenous antibiotics, supportive treatment for pancreatitis. Patients were subjected to routine biochemical investigations, imaging modalities like ultrasound abdomen, and contrast-enhanced computed tomography to detect complications of pancreatitis. The severity of pancreatitis was graded as mild, moderate and severe according to days of hospitalization required and complications of pancreatitis. Mild post-ERCP pancreatitis was defined as requiring an unplanned admission or prolongation of hospitalization by 2–3 days. Moderate post-ERCP pancreatitis as requiring hospitalization of 4–10 days and severe post-ERCP pancreatitis as requiring hospitalization of greater than 10 days or requiring intensive care or intervention for local complications of pancreatitis. The secondary end

point of the study was to assess the severity of post-ERCP pancreatitis in both the groups.

STATISTICAL ANALYSIS

For the analysis of primary end point, we used Fisher exact test to analyze the difference in proportion of patients with post-ERCP pancreatitis in rectal diclofenac and placebo group with p value <0.05 indicating significant difference. Patient's demographic and clinical factors were compared using Fisher exact test or χ^2 test as appropriate.

RESULTS

A total of 400 patients entered the study; 200 patients received rectal diclofenac while 200 patients received glycerin suppository (control group). There were 128 (64%) female patients in rectal diclofenac group while 123 (61.5%) in placebo group. The mean age in rectal diclofenac group was 45.44 years while in placebo group was 47.86 years. The patients in both the group were well matched for the indication of ERCP (Table 1). We compared various risk factors prior to or during the procedure which might increase the risk of post-ERCP pancreatitis like pancreatic cannulation, precut sphincterotomy, suspected sphincter of Oddi dysfunction, pancreatic sphincterotomy, pancreatic duct injection, balloon sphincteroplasty in patients with suspected sphincter of Oddi dysfunction, difficult of failed cannulation in both the groups. The incidences of these various risk factors were similar in both the groups (Table 2). The baseline characteristics of the patients in both the groups were identical (Table 2). Total of 23 patients 12 in placebo group and 11 patients in rectal diclofenac group received pancreatic stents due to recurrent pancreatic duct cannulation or pancreatic duct injection with acinarization. Incidence of post-ERCP pancreatitis was compared in both the groups. 29 out of 400 (7.2%) patient developed post-ERCP pancreatitis. 6 out of 200 (3%) patients in rectal diclofenac group developed post-ERCP pancreatitis compared to 23 out of 200 (11.5%) patients in placebo group (chart 1). Two tailed Fissure exact test was applied. The difference was statistically significant with p value < 0.05. In a subgroup analysis, incidence of post-ERCP pancreatitis in patients with suspected sphincter of Oddi dysfunction in rectal diclofenac group was 6% (4/66) while in placebo group was 18.8% (13/69). Among patients who received pancreatic stent only one patient in rectal diclofenac group (1/11) developed post-ERCP pancreatitis compare to two patients in placebo group(2/12), however number of patients in which pancreatic stenting was performed were low in our study. The secondary endpoint of the study was to assess for severity of post-ERCP pancreatitis in both the groups. The severity of post-

Table 1: Patient details about indication of ERCP

Indication of ERCP	Rectal diclofenac group (n=200)	Placebo group (n=200)	P value
Gall bladder stones (with dilated CBD)	25	27	>0.05
Common bile duct stones	52	57	>0.05
Post cholecystectomy	20	18	>0.05
Malignancy (gall bladder, periampullary, cholangio carcinoma)	21	16	>0.05
ERCP +Suspected sphincter of Oddi dysfunction	66	69	>0.05
Common bile duct stricture (including those with chronic pancreatitis)	16	13	>0.05

Table 2: Characteristic of patients at baseline.

Characteristic	Rectal diclofenac group (n=200)	Placebo group (n=200)	P value
Mean age-yr	45.44	47.86	>0.05
Female sex – no. (%)	128 (64%)	123 (61.5%)	>0.05
Suspected sphincter of Oddi dysfunction (%)	66 (33%)	69 (34.5%)	>0.05
Precut sphincterotomy (%)	21 (10.5%)	24 (12%)	>0.05
Pancreatic duct cannulation (%)	26 (13%)	24 (12%)	>0.05
Pancreatic acinarization (%)	9 (4.5%)	8 (4%)	>0.05
History of recurrent pancreatitis (%)	40 (20%)	35 (17.5%)	>0.05
History of post ERCP pancreatitis (%)	6 (3%)	5 (2.5%)	>0.05
Pancreatic sphincterotomy (%)	11 (5.5%)	12 (6%)	>0.05
Ampullectomy	None	None	>0.05
Difficult cannulation (%)	61 (30.5%)	66 (33%)	>0.05
Pancreatic duct stenting (%)	11 (5.5%)	12 (6%)	>0.05

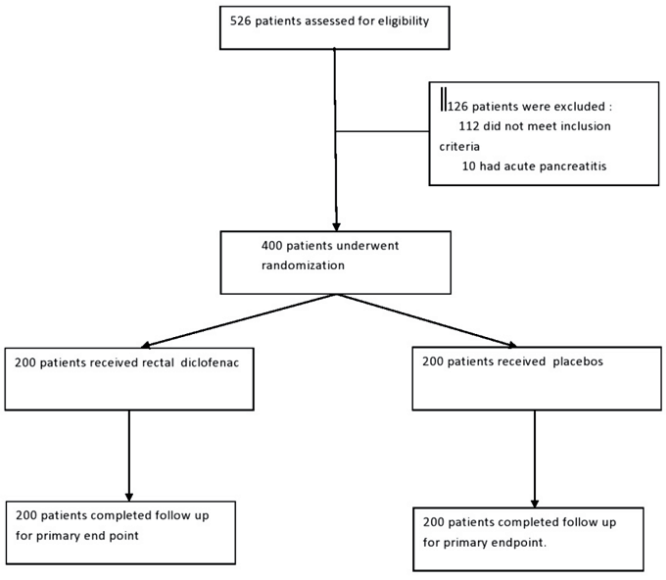

Figure 1: Patient Flow chart.

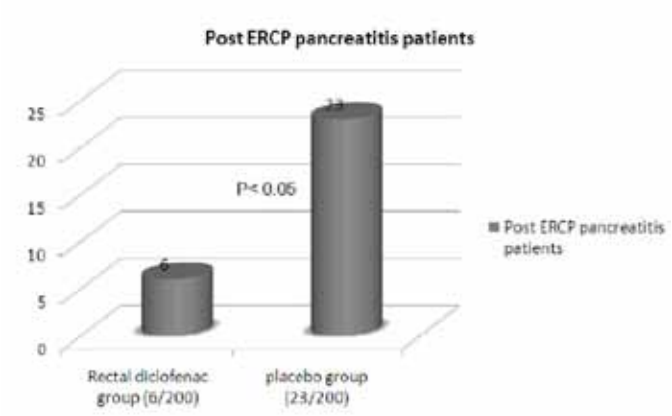

Figure 2: Post-ERCP pancreatitis cases.

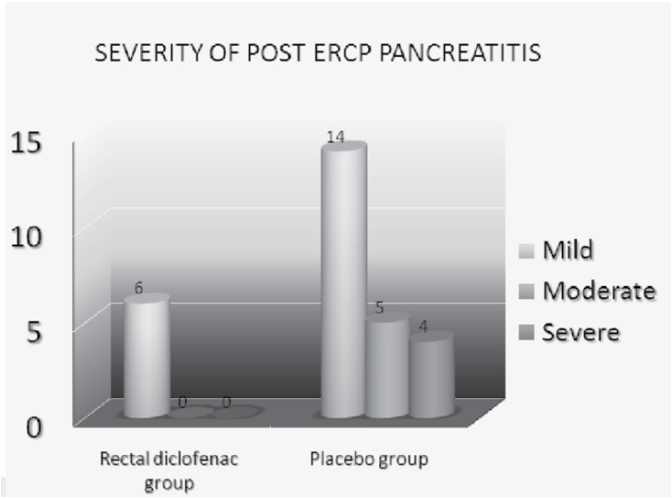

Figure 3: Severity of post-ERCP Pancreatitis.

ERCP pancreatitis in rectal diclofenac group was mild in all six patients (100%), while in placebo group it was severe in four patients (4/23, 17.3%), moderate in five patients (5/23, 21.7%) and mild in 14 patients (14/23, 60.8%) (Figures 2 and 3). The difference in severity of pancreatitis in rectal diclofenac and placebo group was statistically significant. Two out of four patients in placebo group who had severe post-ERCP pancreatitis group developed pancreatic pseudocyst but managed conservatively. One out of four patients in placebo group with severe post-ERCP pancreatitis developed right sided pleural effusion requiring therapeutic pleural tapping. One out of four patients in placebo group with severe post-ERCP pancreatitis developed sub acute intestinal obstruction. Two deaths occurred in the placebo group, both in placebo group with severe post-ERCP pancreatitis, one with right sided pleural effusion and other with sub acute intestinal obstruction. Adverse event, like bleeding while ERCP in sphincteromized patients, was noted in 16 patients; six in placebo group and ten patients in rectal diclofenac group which responded to adrenaline injection and coagulation. All of these patients had minor bleeding and did not required blood transfusion. Rectal diclofenac suppository was well tolerated in all the patients with no adverse event noted with use of rectal diclofenac.

DISCUSSION

Our study has shown that single dose administration of rectal diclofenac prior to or during the procedure has reduced the incidence of post-ERCP pancreatitis. It also has profound impact on reducing the severity of post-ERCP pancreatitis. Majority of our patients had suspected sphincter of Oddi dysfunction. In subgroup analysis our study has shown that rectal diclofenac was also effective in this group of patient in reducing post-ERCP pancreatitis. Rectal diclofenac is a cheap drug, easily available and with a favorable side effect profile. It is underutilized in routine clinical practice. Pancreatic stents are of proven benefit in preventing post-ERCP pancreatitis [8, 9] but difficult to use in routine practice because of difficulty in pancreatic duct cannulation and it require operator expertise. Comparatively, rectal diclofenac is very easy to administer and is easily available. Peak concentration of rectal diclofenac reaches between 30 and 90 minutes after insertion with complete bioavailability. The elimination half life is two hours. Rectal diclofenac has been evaluated in different randomized clinical trials. In a study by Murray et al. [10], 220 patient with high risk of post-ERCP pancreatitis were randomized in two groups, rectal diclofenac versus placebo. In these patients rectal diclofenac was given immediately after the procedure. There was significant reduction in incidence of post-ERCP pancreatitis in rectal diclofenac group as compared to placebo which was similar to our study. However in this study there was no significant difference in patients with sphincter of Oddi dysfunction in rectal diclofenac vs placebo group. Our study demonstrated that there is significant reduction in incidence of post-ERCP pancreatitis even in patients with suspected sphincter of Oddi dysfunction. Khosbaten et al. [11] evaluated the use of rectal diclofenac in patients with extrahepatic cholestasis undergoing ERCP. This study included 100 patients which were randomized into rectal diclofenac and placebo group. This study also reported significant reduction in incidence of post-ERCP pancreatitis in rectal diclofenac group similar to our study. However this study has reported very high incidence of post-ERCP pancreatitis (26%) in the control group. Oral diclofenac has been evaluated for prevention of post-ERCP pancreatitis by Cheon et al., but was found to be of no benefit [12]. Meta-analysis by Elmunzer et al. [13]. has concluded that NSAIDs were effective in preventing post-ERCP pancreatitis, however, additional multicenter studies are needed for confirmation prior to widespread adoption of this strategy. Though rectal diclofenac is such an attractive option in prevention of post-ERCP pancreatitis it is still underutilized. There are

very few trials evaluating its use in prevention of post-ERCP pancreatitis. There is no Indian data available on use of rectal diclofenac for prevention of post-ERCP pancreatitis to the best of our knowledge till date. This prospective single centre, open labeled randomized placebo controlled trial has shown that use of single dose of rectal diclofenac immediately prior to or during the ERCP in high risk patients is effective in not only reducing the incidence but also severity of post-ERCP pancreatitis. It is also effective in patients with suspected sphincter of Oddi dysfunction. The major limitation of this study was severity of pancreatitis was graded according to the consensus guideline depending on days of hospitalization and complications. Various scoring system like Ranson's score, APACHE II score were not utilized. However similar guidelines were followed in previous studies.

CONCLUSION

Rectal diclofenac prior to or during ERCP (endoscopic retrograde cholangiopancreatography) in high risk patient reduces the incidence as well as severity of post-ERCP pancreatitis compared to placebo.

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Author Contributions
Sandeep Patil – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Vikas Pandey – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Nilesh Pandav – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Meghraj Ingle – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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