ORIGINAL ARTICLE

EFFICACY OF DICLOFENAC SODIUM VERSUS SOMATOSTATIN FOR THE PREVENTION OF PANCREATITIS IN PATIENTS UNDERGOING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Adel Hamed Elbaih[1], Mohammed Elsayed Mohammed[2], Mohammed Mahmoud Abdo[3], Khalil Ali Khalil[4]

Author's Affiliations: [1]Assistant Professor, Department of Emergency Medicine; [2]Assistant lecturer, [3]Assistant Professor, [4]Professor, Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
Correspondence: Dr. Adel Hamed Elbaih E-mail: elbaihzico@yahoo.com

ABSTRACT

Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure performed with a side view scope that can be either diagnostic or therapeutic. Endoscopic procedure as with other medical procedures has both minor and major complications. The most common major complication of ERCP is pancreatitis, with a prevalence of 1% to 40%.

Aim: to assess the efficacy of diclofenac sodium versus somatostatin for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP).

Methods: the present study was carried out as an interventional study on 75 patients with evidence of biliary obstruction accepted for ERCP, divided into 3 groups. Group I included 25 patients as control group, group II included 25 patients who were administered 100 mg of diclofenac sodium administered rectally 30 minutes before ERCP and group III included 25 patients who were administered a single bolus injection of 250 mcg somatostatin 30 minutes before ERCP and these groups were compared regarding efficacy of diclofenac sodium versus somatostatin for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Results: there was no statistically difference between the study groups as regards the occurrence of post-ERCP pancreatitis. The incidence of post-ERCP pancreatitis was 13.3%. Post-ERCP pancreatitis occurred in 5 cases (20%) of the first group, 2 cases (8%) of the second group, 3 cases (12%) of the third group. No risk factors for post-ERCP pancreatitis were statistically significant.

Conclusion: there was no statistically difference between the study groups as regards the occurrence of post-ERCP pancreatitis.

Keywords: ERCP, pancreatitis, Diclofenac sodium, Somatostatin

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure performed with a side view scope that can be either diagnostic or therapeutic. This endoscopic procedure as with other medical procedures has both minor and major complications. The most common major complication of ERCP is pancreatitis, with a prevalence of 1% to 40%.[1]

According to a consensus proposed by Cotton et al. in 2009, Post-ERCP pancreatitis (PEP) is the presence of new pancreatic-type abdominal pain severe enough to require hospital admission or prolonged hospital stay with levels of serum amylase three times greater than normal, occurring 24 hours after ERCP. Post-ERCP pancreatitis is graded as mild, moderate, or severe, depending on the number of days of hospitalization required and on the level of necessary intervention: (1) Mild: serum amylase at least three times normal at more than 24 hours after the procedure, requiring admission or prolongation of planned admission to 3 days; (2) Moderate: hospitalization of 4-10 days; and (3) Severe: hospitalization of more than 10 days, or hemorrhagic pancreatitis, phlegmon, or pseudocyst, or required intervention (percutaneous drainage or surgery). [2,19]

According to Atlanta classification in 2002, the diagnosis of PEP requires two of the three following cri-

teria: (i) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (ii) serum lipase or amylase activity at least three times greater than the ULN; and (iii) characteristic findings of acute pancreatitis on contrast-enhanced CT and, less commonly, magnetic resonance imaging or transabdominal ultrasonography. This classification defines three degrees of severity based on the presence or absence of organ failure (plus its duration) and of local or systemic complications. [3]

In experimental models of acute pancreatitis it has been suggested that digestive enzyme activation might occur within acinar cells and it has been shown that in the early stages of acute pancreatitis, there is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles. This co-localization mechanism might result in the activation of the digestive enzymes, mainly trypsin. [4]

Other possible causes of post-ERCP pancreatitis are the introduction of activated intestinal enzymes and bacteria into the pancreatic ductal system by ERCP maneuvers. If enzyme activation and bacterial infection are causes of post-ERCP pancreatitis (PEP), enzyme inhibitors and antibiotic prophylaxis might have a therapeutic role. [4]

Until this time, routine prophylaxis has not been adopted in the majority of centers that conduct ERCP procedures or recommended in guidelines. This means that most endoscopist in the ERCP field believe that expertise and technique more than pharmacologic prophylaxis play a major role in the prevention of post procedure pancreatitis. [5]

From the literature, potential drugs for prevention of PEP include somatostatin, octreotide (a long-acting somatostatin analog), gabexate mesilate, nitroglycerin, calcium-channel blocker, N-acetylcysteine, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs; indomethacin and diclofenac), allopurinol, interleukin- 10, platelet-activating factor inhibitor, tumor necrosis factor-α inhibitor, and antibiotics. [6]

The simplest agent for interrupting the inflammatory cascade is the NSAIDs that can inhibit the early inflammatory cascade involving phospholipase-A2, prostaglandins, or endothelial neutrophil attachment during acute pancreatitis. Inhibition of exocrine pancreatic secretion can be obtained by somatostatin and its synthetic analogue, octreotide. The hormone and its analogue affect the exocrine function both directly, by reducing the secretion of digestive enzymes, and indirectly, by inhibiting secretin and cholecystokinin production. [7]

A number of specific risk factors acting independently or in concert have been proposed as predictors of post-ERCP pancreatitis. These include both patient and procedure-related factors. So and after all of this; the present study aims to assess the efficacy of diclofenac sodium versus somatostatin for prevention of post-endoscopic retrograde cholangio-pancreatography (ERCP) pancreatitis to find simple and economic medical prophylaxis to be used routinely in all patients accepted for ERCP without harmful side effects.[8]

METHODOLOGY

Study Design and Site: The present study was carried out as an interventional study aiming to assess the efficacy of diclofenac sodium versus somatostatin for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. The work was carried out in the emergency medicine department and endoscopy unit of Suez Canal university hospitals.

Study population: This study was carried out on 75 patients divided into 3 groups, each group included 25 patients. All Patients with evidence of biliary obstruction accepted for ERCP and give consent to participate in the study without affecting their course of treatment accordingly permission obtained from ethical committee of faculty of medicine in Suez canal university and All Patients were included according to the following:

Inclusion criteria

1. All patients aged 18 years and above.
2. Patients with evidence of biliary obstruction.
3. No sensitivity or contraindications to diclofenac sodium or Somatostatin.

Exclusion criteria

1. Established pancreatitis before ERCP.
2. Anatomical changes due to previous surgeries.
3. Pregnancy.
4. Recent use of NSAIDs or Somatostatin.
5. Renal impairment.

Patients were assessed through these items:

Study group: Patients who matched the inclusion criteria were included through the study and were divided into 3 groups:

Group 1 (control group)
Group 2 (patients who were administered diclofenac sodium)
Group 3 (patients who were administered somatostatin)

Questionnaire:

1. **Sociodemographic data:** concerned with sex, age, presence of chronic illness.
2. **Patients related risk factors:** as history of previous post-ERCP pancreatitis, history of previ-

ous pancreatitis, presence of abdominal or biliary pain, past or presenting cholangitis or prior cholecystectomy.

General Examination: including weight in kilo gram (kg), height in centimeters (cm) and body mass index (BMI).

Laboratory investigations: laboratory findings related risk factors as TLC, serum amylase, serum triglycerides, serum calcium, ALP, ALT, AST, serum total bilirubin, and serum direct bilirubin.

Radiological investigations: abdominal C.T, U.S findings related risk factors in the form of common bile duct stones, gall bladder stones and CBD >10 mm.

ERCP:

1. **ERCP findings related risk factors:** in the form of common bile duct stones, CBD >10 mm and Periampullary diverticulum.
2. **Procedure related risk factors:** biliary stenting, stone extraction either by balloon sweeping or basket and failed cannulation.
3. **Indication for the procedure:** obstructive jaundice or biliary colic.
4. **Final diagnosis of ERCP:** CBD stones, CBD stricture or obstructed stent.
5. **Post-ERCP pancreatitis:** between present or not present.

The study passed into 3 main stages:

1- Pre-intervention

All groups were:

1- Assessed clinically to exclude signs and symptoms of pancreatitis.
2- Applying the previous mentioned items.
3- Serum amylase was measured pre-ERCP.

2- Intervention

1- Group 1; control group.
2- Group 2; were administered 100 mg of diclofenac sodium administered rectally 30 minutes before ERCP.
3- Group 3; were administered a single bolus injection of 250 mcg somatostatin 30 minutes before ERCP.
4- ERCP was done by the same endoscopist.

3-Post intervention

1- Patients were re-assessed clinically again to determine signs or symptoms of pancreatitis.

2- Serum amylase was measured post ERCP;

- Values less than 1.5 times the upper limit of normal (ULN), obtained at 2–4 hours post-ERCP, almost exclude Post ERCP Pancreatitis.

- Values more than 3 times the ULN at 6 hours post-ERCP were considered as PEP

RESULTS

The present study included 75 patients with BMI of patients in the study the mean was 25.05. And the sociodemographic among study found Males constituted 44% of the study population while females constituted 65%.The age ranged from 18-79 years with the mean of 52 years the chronic illnesses in patients of the study. Diabetes was the main systemic disease (22.7%) followed by hypertension (14.7%) shows with the indication of the procedure. 62.7% of the patients had obstructive while 37.3% had biliary colic.

Table 1: Patient related risk factors

Variable	No. (%)
History of previous post-ERCP pancreatitis	2 (2.7)
History of previous pancreatitis	3 (4)
Abdominal or Biliary pain	63 (84)
Past or presenting cholangitis	23 (30.7)
Prior cholecystectomy	11 (14.7)

Table (**1**) shows the patient related risk factors. 2.7% of the patients had history of previous post-ERCP pancreatitis. 4% of the patients had history of previous pancreatitis. 84% of the patients complained of abdominal or biliary pain. 30.7% of the patients had history of past or presenting cholangitis. 14.7% of the patients had history of prior cholecystectomy.

Table 2: Pertinent laboratory results before ERCP

Lab. Investigation	Range	Mean ± SD
Amylase	12-165	64.10±34.12
TLC	3-21	8.92±4.34
Total bilirubin	0.3-34	6.94±7.05
Direct bilirubin	0.1-26	5.85±6.01
ALT	6-868	133.46±148.88
AST	8-447	94.90±76.59
ALP	28-1489	389.26±270.84
Serum triglycerides	104-325	196.98±66.47
Serum calcium	7.2-10.2	8.72±0.64

Pertinent laboratory results before and after ERCP in the study was shown in **tables (2), (3).** Serum amylase levels ranged from 12-165 mg/dl with the mean of 64 mg/dl before ERCP. 6 hours after ERCP, the level ranged from 16-1500 mg/dl with the mean of 201 mg/dl. And abdominal C.T, U.S and ERCP findings. 53% of the patients had CBD. 56% of the patients had gallbladder. 68% of the patients had CBD > 10 mm.

Table 3: Pertinent Laboratory results after ERCP

Investigation	Range	Mean ± SD
Amylase	16-1500	201.73±293.13
TLC	3.2-19	8.75±3.77
	No. (%)	
CBD stones	40 (53)	
Gallbladder stones	42 (56)	
CBD >10 mm	51(68)	
Periampullary diverticulum	11 (14.7)	

Table 4: Procedure related risk factor with Final diagnosis of ERCP

Diagnosis		No. (%)
Biliary stenting		50(66.7)
Stone extraction	Balloon	23(30.7)
	Basket	0(0)
Failed cannulation		3(4)
CBD stones		52 (69.3)
CBD stricture		14 (18.7)
Obstructed stent		9 (12)

Table 5: Incidence of post-ERCP pancreatitis in the study groups

Variable	Post-ERCP pancreatitis (%)	P Value
Control	5 (20)	
Diclofenac	2 (8)	0.446
Somatostatin	3 (12)	
Total	10 (13.3)	

Table 6: Risk factors and incidence of post-ERCP pancreatitis in the study groups

Variable	No. (%)	p-Value
Sex		
Male	4 (9.5)	0.274
Female	6 (18.2)	
Age		
<60 years	7 (15.9)	0.434
>60 years	3 (9.7)	
Patient related risk factors		
History of previous post-ERCP pancreatitis	0 (0)	0.574
History of previous pancreatitis	0 (0)	0.488
Prior cholecystectomy	1 (9.1)	0.654
USG and CT findings		
CBD >10 mm	6 (11.8)	0.560
Diagnosis of ERCP		
CBD stones	8 (15.4)	
CBD stricture	2 (14.3)	0.453
Obstructed stent	0 (0)	
Total bilirubin		
Normal	3 (25)	0.195
Abnormal	7 (11.1)	

Table (4) shows procedure related risk factors. Biliary stenting was done in 66.7% of the patients. Stone extraction was done by balloon sweeping in 30.7% of the patients. Cannulation failed in 4% of the patients. And the final diagnosis of ERCP. 69.3% of ERCP was diagnosed as CBD stones; 18.7% was diagnosed as CBD while 12% was diagnosed as obstructed stent.

Table (5) show the incidence of post-ERCP pancreatitis in the study groups. The incidence of post-ERCP pancreatitis was 13.3%. Post-ERCP pancreatitis occurred in 20% of the control group, 12% of diclofenac group, 8% of somatostatin group. This difference was not statistically significant.

Table (6) shows risk factors and incidence of post-ERCP pancreatitis in the study groups. No risk factors were statistically significant.

DISCUSSION

This study was an interventional study aiming to assess the efficacy of diclofenac sodium versus somatostatin for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. The study was carried out in the endoscopy unit of Suez Canal University hospitals through studying 75 patients aged 18 years and above presented with evidence of biliary obstruction according to inclusion and exclusion criteria as mentioned before. In our study, we found that the incidence of post-ERCP pancreatitis was 13.3%. This is similar to what was reported by Matsushita et al. [9] who showed that post-ERCP pancreatitis have ranged from 1% to 15.1%. This is higher than what was reported by Andriulli et al. [10]who reported a rate as 3.47 %. A recent meta-analysis of 108 randomized, controlled trials (RCTs) reported an overall incidence of 9.7%. Another study by Wong Let al. [12] reported a rate as 5.4%. In our study, we found that pancreatitis occurred in 20% in the control group, 8% in the second group in which patients were administered diclofenac sodium and 12% in the third group in which patients were administered somatostatin. This difference was not statistically significant.

Our results disagree with what was reported by Wong L et al. [12]. Who studied 220 patients with high risk of post-ERCP pancreatitis 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. However in this study there was no significant difference in patients with sphincter of Oddi dysfunction in rectal diclofenac vs placebo group. Wong L et al. [12] evaluated the use of rectal diclofenac in patients with extrahepatic cholestasis un-

dergoing ERCP. This study included 100 patients randomized into rectal diclofenac and placebo group. This study also reported significant reduction in incidence of post-ERCP pancreatitis in rectal diclofenac group. Our results disagree with what was reported by Andriulli et al. [10] in 2000 in which they conducted a meta-analysis reviewing the prophylactic effects of somatostatin on PEP and showed the preventive efficacy of somatostatin. Seven years later, Andriulli et al. [10] updated their meta-analysis by including nine high-quality trials on somatostatin, reported that somatostatin cannot reduce the incidence of PEP, whereas significant efficacy was obtained only in the subgroup of patients who received somatostatin as a bolus injection.

Almost around the same period, Rudin et al. [14] also performed a meta-analysis of five somatostatin studies, demonstrated that somatostatin can significantly decrease the PEP rate with an infusion for 12 hours or more as well as for bolus infusion, with risk differences of 7.7and 8.2 respectively. Another RCT [15] of 391 patients in whom therapeutic ERCP was undertaken showed that the incidence of PEP was significantly lower in the group in which somatostatin administration was continued for 12 hours starting from 30 minutes before ERCP (3.6 % in the treatment group vs. 9.6 % in the placebo group). In 2010, Thomas PR et al. [16] summarize 17studies about the preventive efficacy of somatostatin and octreotide for PEP and suggested significant efficacy. They stated that somatostatin and high-dose octreotide may prevent PEP. That meta-analysis also reported that the preventive efficacy of somatostatin is more prominent in cases of pancreatic duct injection, or balloon sweeping, or high-dose administration over 12 hours, or bolus injection. In our study, younger age was not significantly associated with a high risk for pancreatitis. This is in agreement with a recent study revealed that age of 60 years or less is not associated with any clinically significant risk for PEP. [17] Another study reported that age less than 25 years was a high risk factor for PEP. [16] Our results is not consistent with different studies showing that younger age was found to be a significant risk by univariate analysis but not by multivariate model.[19]There was an inverse relationship between the age and the occurrence of PEP (the younger the patient, the higher the percentage of pancreatitis). Younger age was first identified as an independent risk factor for PEP in a multicenter study in 1996, and subsequently confirmed in four other multivariate analyses. [20] The higher risk in these studies may be explained by the progressive decline in pancreatic exocrine function with aging that may protect older patients from pancreatic injury. [20]Nishino et al. study concluded that one of the patient-related risk factors was age more than 65 years.

In our study, female sex was a nonsignificant risk factor for PEP and this result is in agreement with Testoni et al. [17] in which female sex was not associated with any clinically significant risk for PEP. Our results disagree with a large multicenter study [2] in which female sex was a significant risk factor for PEP in univariate but not in multivariate analysis. Our study disagrees with the studies reporting that female individuals appear to be at higher risk for developing postprocedural pancreatitis compared with male individuals in both univariate and multivariate analysis.[11] However, most previous studies have demonstrated a higher risk in patients with sphincter of Oddi dysfunction (SOD), a condition that occurs primarily in women. [11] In our study, none of patients included in our study with history of previous pancreatitis and history of previous post-ERCP pancreatitis developed pancreatitis. This is similar to a recent multivariate study that revealed history of PEP was not a significant risk factor for PEP. [17]

In contrast, several recent multivariate risk factor studies stated that past history of pancreatitis was a highly significant risk factor for PEP. Testoni et al. [17], revealed that history of previous pancreatitis is only a significant risk factor by univariate analysis. In addition, several multivariate risk factors studies stated that history of previous PEP was found to be a highly significant factor for PEP. [19] The previous two findings suggest that certain individuals have a 'reactive' pancreas that places them at particular risk beyond that conferred by other definable risk factors. [21] In our study, history of previous cholecystectomy was found to be insignificant risk factor for PEP. This result is in agreement with a recent multivariate study. In contrast, the results obtained by Todd HB et al. [1] showed that prior cholecystectomy is a significant risk factor for PEP in univariate but not in multivariate analysis. In our study, normal bilirubin level at the time of ERCP was not significantly associated with an increase in the risk for PEP. Some studies showed that normal bilirubin level at the time of ERCP would independently increase the risk for PEP; another one showed that normal bilirubin was not associated with any clinically significant risk for PEP. [19] Most studies agreed that hyperbilirubinemia is not a risk factor for pancreatitis. In our study, common bile duct diameter was insignificant risk factor for PEP. This result is in agreement with most studies that have found no independent influence of duct size on the risk for PEP. [19] In contrast, many early studies suggested small CBD diameter as a risk factor for pancreatitis. In our study, no significant difference was found between benign and malignant nature of the disease with respect to PEP. This result is in agreement with the only study comparing the relationship of nature of the disease and PEP. [21]

So in the end we find Endoscopic retrograde cholangiopancreatography (ERCP) is an important tool to

diagnose and treat hepatobiliary disorders. Although magnetic resonance cholangio pancreatography (MRCP) offers a noninvasive technique to diagnose these disorders, ERCP still represents the broadest range of diagnostic and therapeutic options. Pancreatitis represents the commonest post-ERCP complication. Although usually mild, sometimes it may be severe and warrants admission to ICU and may end fatally. Several trials were made to reduce such complication including drugs or pancreatic duct stenting. As regards the use of drugs, somatostatin, NSAIDS, gabexate, nitroglycerine have all been studied with debating results. In the present study we tried to study the efficacy of diclofenac sodium versus somatostatin for prevention of post-ERCP pancreatitis. Pharmacological prevention of pancreatitis after ERCP has been the topic of several investigations in recent years but still remains a debate question.

The incidence of post-ERCP pancreatitis was 13.3%. Post-ERCP pancreatitis occurred in 5 cases (20%) of the first group, 2 cases (8%) of the second group, 3 cases (12%) of the third group and this difference was not statistically significant. Risk factors for post-ERCP pancreatitis were also not statistically significant.

CONCLUSION

At the end of the study, we can conclude that there was no statistically difference between the study groups as regards the occurrence of post-ERCP pancreatitis. We also can conclude that no risk factors for post-ERCP pancreatitis were statistically significant.

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