

## THE ROLE OF PROPHYLACTIC OCTREOTIDE IN PREVENTING ERCP INDUCED PANCREATITIS

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### ABSTRACT

#### BACKGROUND

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is a technique that uses a combination of luminal endoscopy and fluoroscopic imaging for diagnosis and treatment of pancreato-biliary system disorders. ERCP also has its own adverse effects which can be mild to severe and even life threatening.<sup>1,2</sup> The common side effects of ERCP are: • Pancreatitis. • Haemorrhage. • Perforation. • Cholangitis. In this study, we are going to assess the role of prophylactic octreotide in preventing ERCP induced pancreatitis.

The objectives of the study were-

1. To find out the incidence of post-ERCP pancreatitis.
2. To evaluate the role of octreotide in preventing post-ERCP pancreatitis.

#### MATERIALS AND METHODS

In the period of study of 6 months, 240 patients who underwent ERCP were assessed for eligibility. Out of them, 127 patients were excluded from the study depending on the exclusion criteria. The rest 113 patients were randomized into two groups, the group A of 55 patients was assigned to patients who were given octreotide doses and a group of 58 patients was given 0.9% NS as placebo. The randomization was done using computer generated methods that randomized each subject to a single treatment by using the method of randomly permuted blocks.

**Settings and Design-** Inpatient male and female wards of the Department of General Surgery at a single center undergoing ERCP procedure in the Department of Medical Gastroenterology in a tertiary care center. We conducted a prospective, single center, open labelled, randomized placebo-controlled trial evaluating the role of prophylactic octreotide in the prevention of post-ERCP pancreatitis in patients undergoing the procedure and whether it has any implications on the severity of post-ERCP pancreatitis. The study was conducted over a period of six months.

#### RESULTS

There was a decrease in the incidence of Post ERCP pancreatitis in the group receiving octreotide (in the proposed dosage form and schedule) but the same was not statistically significant.

#### CONCLUSION

From an initial era of diagnosis and therapeutics to current times where the focus lies on safer techniques and refined procedure with good clinical outcome, ERCP has changed our understanding of the various hepatobiliary and pancreatic pathologies. Hence, focusing on adverse effects and finding methods to prevent the same has been a thrust area in this field. Pharmacologic prevention of pancreatitis which is one of its most common complications has brought forward various drugs including octreotide into trials.

#### KEYWORDS

Post ERCP Pancreatitis (PEP), Octreotide.

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#### BACKGROUND

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is a technique that uses a combination of luminal endoscopy and fluoroscopic imaging for diagnosis and treatment of pancreato-biliary system disorders. It is now well established and has changed the diagnosis and management protocols of hepato-biliary and pancreatic diseases. Like any other interventional procedure, ERCP also has its own adverse effects which can be mild to

severe and even life threatening.<sup>1,2,3</sup> The common side effects of ERCP are:

- Pancreatitis
- Haemorrhage
- Perforation
- Cholangitis
- Stent- related adverse events
- Cardiopulmonary adverse events
- Miscellaneous Adverse events

There is a 3-5% incidence of pancreatitis, as shown in various large studies.<sup>2,4</sup> A systematic survey of 21 studies involving 16855 patients (1987-2003) found a 3.5% occurrence of Post-ERCP Pancreatitis (PEP). 0.4% of patients had severe pancreatitis with 0.11% deaths.<sup>5</sup> Hence, the minimization of both the incidence and severity of PEP is paramount. Various studies have been conducted to focus on risk factors and subsequent prophylactic measures to reduce the incidence and also in prompt diagnosis and early treatment of this adverse event.<sup>3</sup> Various theories regarding pathogenesis of PEP have been put forward—

- Mechanical factors including transient obstruction to outflow of pancreatic secretion due to trauma to papilla and pancreatic sphincter (considered as most important factor).<sup>6</sup>
- Hydrostatic factors where injection of contrast or saline causes increased pressure and parenchymal injuries with increased secretion of pancreatic enzymes leading to inflammation.
- Other postulated factors include, enzymatic injury from the released enzyme from the pancreatic secretions during procedure, chemical injury due to possible allergy to contrast injected and infection from the contaminated endoscopes, cannula and other instruments used in the procedure.<sup>6,7</sup>

Most drugs studies aimed at preventing PEP target the inflammatory cascade caused by proteolytic enzymes, either by decreasing production of pancreatic enzymes, inhibiting proteolysis, or decreasing intraductal pressure from pancreatic secretion. Somatostatin decreases pancreatic enzyme secretion by Octreotide, a synthetic analogue of somatostatin, has a much longer half-life. The pharmacologic effects of octreotide are similar to those of somatostatin, a hypothalamic peptide. It acts over the somatostatin receptor though the exact mechanism of action is not known. It inhibits the secretion of both pituitary and gastrointestinal hormones including serotonin, gastrin, secretin, motilin, pancreatic polypeptide, growth hormone and thyrotropin. With the diverse number of hormones affected by octreotide, its actions are diverse. It decreases secretion of pancreatic enzymes, reduces intraductal pressure, and possibly proteolysis. There have been conflicting evidences to whether doses of octreotide could help in prevention of post ERCP pancreatitis. In the latest European society of Gastrointestinal Endoscopy Guideline-Updated June 2014, role of octreotide has been

reserved to high risk groups undergoing ERCP procedure with limited data about the effects of the same in higher doses and comparison between infusion versus bolus doses and subcutaneous versus intravenous doses.<sup>8,9</sup>

#### **Aims and Objectives**

- To find out the incidence of Post-ERCP pancreatitis
- To evaluate the role of octreotide in preventing post-ERCP pancreatitis.

#### **Inclusion Criteria**

Male and female patients who are-

1. More than 18 years of age.
2. Willing to participate in the study.
3. Undergoing ERCP for a valid indication.
4. Following up with post-ERCP evaluation for diagnosing PEP.

#### **Exclusion Criteria**

1. Patients who are having-
2. Age less than 18 years.
3. Pregnancy or lactation.
4. Chronic renal failure.
5. Acute myocardial infarction during the last 3 months before procedure.
6. HIV positive or any other immune compromised state.
7. Planned biliary stent removal or exchange.
8. History of alcohol or other drug abuse.
9. History of chronic pancreatitis or other disease is known to affect pancreatic secretion (vagotomy, gastrectomy, inflammation).
10. Refusal to participate.
11. Patient with the previous history of ERCP-induced pancreatitis.

#### **MATERIALS AND METHODS**

**Ethics-** The study was initiated after obtaining the approval of The Institutional Ethics Committee as per Ethical Guidelines for Biomedical Research on Human subjects, Indian Council of Medical Research, New Delhi, 2006. Written informed consent was taken from all participating patients or their legally accepted representative. The study was also registered under the Clinical Trial Registry of India.

**Settings-** Inpatient male and female wards of the Department of General Surgery at a single center undergoing ERCP procedure in The Department of Medical Gastroenterology in a tertiary care center.

**Study Design-** We conducted a Prospective, single center, open labelled, a randomized placebo-controlled trial evaluating the role of prophylactic octreotide in the prevention of post-ERCP pancreatitis in Patients undergoing the procedure and whether it has any implications on the severity of post-ERCP pancreatitis. The study was conducted over a period of six months.

## Methodology

In the period of study of 6 months, 240 patients who underwent ERCP were assessed for eligibility. Out of them, 127 patients were excluded from the study depending on the exclusion criteria. The rest 113 patients were randomized into two groups, the group A of 55 patients was assigned to patients who were given octreotide doses and a group of 58 patients was given 0.9% NS as placebo. The randomization was done using computer generated methods that randomized each subject to a single treatment by using the method of randomly permuted blocks.

## Procedure

Patients in group A were given 3 doses of 100 micrograms of octreotide 12 hours, 6 hours and 45 minutes before the procedure. Patients in group B were given placebo (0.9% NS) in similar dose and duration. The ERCP procedures were performed by two experienced endoscopist operator. During the procedure, an assistant recorded the details of the procedure viz timing of the procedure, the number of pancreatic duct cannulation and injection, difficulty in cannulation, whether precut, pancreatic sphincterotomy, balloon sphincteroplasty was done. After the procedure, patients were given the same dose of octreotide at 6- and 12-hours duration in group A and 0.9% NS in group B. later, all the patients were assessed for any two criteria, as per the modified ATLANTA classification of acute pancreatitis mentioned in detail in the review of the literature.

## They will be assessed in terms of-

- Clinical signs of abdominal pain requiring persistent hospitalization.
- Increase in serum amylase levels three times more than the upper limit of normal
- Radiology finding suggestive of acute pancreatitis

Post procedure patients were admitted for observation. Patients were assessing for any immediate complications, such as abdominal pain, distension. Patients were subjected to testing of serum amylase levels 6 hours and 24 hours post procedure. Those patients who had no abdominal pain, vomiting and back pain were started oral liquids 6 hours post procedure. Primary endpoint of the study was to detect a number of patients developing post-ERCP pancreatitis in both 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 endpoint of the study was to assess the severity of post-ERCP pancreatitis in both the groups. Also, the various procedural techniques and baseline profile of the patients including age, sex Laboratory investigations (Liver function tests) were assessed to identify the risk factors associated with post-ERCP pancreatitis.

## RESULTS

### 1. Age Distribution

Out of the total population studied (n=113), a total of 55 patients (Group A) received a dosage of octreotide. This group had a mean age of 47.55 with a standard deviation of 13.52. The other Group B with a total of 58 patients received 0.9% N.S. as the dose with a mean age group of 47.60 and a standard deviation of 14.14. The mean age group of the patients in our study was 47.17 with a standard deviation (SD) of 13.58

### 2. Gender Distribution

In the Group A, there were 21 (38.18%) males and 34 (61.82%) females. There were 23(39.66) males in Group B with 35(60.34) females. In total, there were 44(38.94%) males and 69(61.06) females in the study.

### 3. Nature of Disease

In Group A 49 (89.09%) patients had a benign disease with 6(10.91%) patients having the malignant disease as an indication for ERCP. In the Group B, 45(77.59%) had a benign disease with 13(22.41%) having malignant disease. A total of 94 (83.19) patients had benign disease and 19 (16.81%) patients had a malignant disease in the whole study.

### 4. Indication for ERCP

Amongst the various indications for which patients underwent ERCP were 5 broad categories were made as shown in table..., CBD stones (Cholelithiasis) was the most common indication with 39(70.91%) patients in group A and 24 (41.38%) in group B. 6 (10.91%) patients in Group A had bile duct injuries and 6(10.34%) in group B. 3 (5.45%) patients had benign CBD strictures all of them in the distal CBD with 7 (12.07%) having malignant CBD strictures. Under malignant CBD strictures, 2 patients had hilar stricture with 1 patient having a mid-CBD stricture and 4 patients having malignant distal CBD stricture. There was 1 (1.82%) patient in Group A with Gallbladder stones with dilated CBD who required ERCP whereas there were 6 patients in Group B with the same indication. Amongst malignancies, 6 (10.91%) patients undergoing ERCP were in Group A and 6 (10.34%) in Group B.

**5. ERCP Techniques**

In Group A 2 (3.64%) patients underwent Precut procedure during ERCP compared to 7 (12.07%) in Group B. 2 (3.64%) patients in Group A underwent PD stenting while 7 (12.07%) underwent the same procedure in Group B. Only 1 (1.82%) underwent pancreatic sphincterotomy in Group A and 1 (1.72%) from Group B. 17 (30.91%) patients underwent Biliary Balloon Dilatation in Group A and 9 (15.52%) in Group. the number of patients undergoing Biliary Sphincterotomy was 44 (80%) in Group A and 41 (70.69%) in Group B.

**6. Baseline Laboratory Investigations**

Investigation	Group 1		Group 2		P-value*
	Mean	SD	Mean	SD	
Bilirubin Total	3.15	2.36	3.90	2.54	0.1073
Bilirubin Direct	2.01	1.23	2.72	2.11	0.0321
SGOT	87.11	19.06	95.74	27.79	0.0581
SGPT	45.65	16.85	52.55	15.15	0.0238
Alk. Phosphatase	173.31	55.72	177.72	48.24	0.6532
Hb	10.53	1.08	10.72	1.11	0.3588
TLC	9076.36	3812.60	9084.48	4129.69	0.9914
PT/INR	1.20	0.21	1.23	0.12	0.35

**Table 1. Laboratory Investigations**

\*Calculated using unpaired t-test. P-value <0.05 considered significant.

Parameter	Group 1		Group 2	
	R	p-value	R	p-value
Bilirubin total	-0.03065	0.8242	-0.15415	0.24796
Bilirubin direct	-0.10754	0.43451	-0.16426	0.2179
SGOT	0.08302	0.54679	0.03726	0.78124
SGPT	-0.14129	0.30351	0.15601	0.24223
Alk. Phosphatase	0.04596	0.73897	0.07617	0.56983
Hb	0.14443	0.29278	-0.07295	0.5863
TLC	-0.11331	0.41011	0.02708	0.84012
PT/INR	-0.10111	0.46265	-0.0678	0.61305

**Table 2. The Baseline Laboratory Investigations in both the Groups- Were Broadly Matched**

\*Calculated using Spearman's correlation coefficient (r). P-value<0.05 is considered significant. When r is >0.75: Good correlation; 0.25-0.75: Intermediate correlation; <0.25: Weak correlation.

**Post Procedure Assessment**

- Abdominal Tenderness - In Group A 7(12.73%) developed abdominal tenderness compared to 48

(87.27%) with no such clinical signs. In Group B 15 (25.86%) had abdominal tenderness post-procedure whereas 443 (74.14%) had no such clinical signs.

- Imaging was done as a diagnostic modality in a total of 80 patients with none suggestive of acute pancreatitis in Group A and 2 (3.45%) suggestive of acute pancreatitis in Group B.
- Serum Amylase levels >3 times the upper limit of normalcy after 24 hours of procedure was also compared. The same was done for 37 patients in Group A with 3 (5.45%) having higher values and 34 (61.82%) having lower values than 3 times the upper limit of normalcy. In Group B, 43 patients underwent the testing in which 8 (13.79%) had a higher value while 35(60.34%) had no significant rise in serum amylase levels.
- Acute pancreatitis Post-ERCP was present in 2 (3.64%) patients in Group A and 6 (10.34%) in Group B. Overall 8 patients had post-ERCP pancreatitis in our study group. The NNT (number needed to treat) value in our study came out to be 14.9 (15). That means on an average 14.9 patients would have to receive a prophylactic dose of octreotide for preventing one outcome of Post-ERCP pancreatitis.
- Severity assessment was also done based on Consensus guidelines as discussed above. 2 patients in Group A developed mild acute pancreatitis whereas 1 patient in Group B developed mild, 3 patients had a moderate course and 2 had a severe course of acute pancreatitis.
- In Complication assessment none of the patients developed nausea post dose administration in Group A with 4 people complaining of nausea in Group B. There was no reported pain at the injection site in both the groups. Both the groups reported no allergic reaction post drug administration.

**DISCUSSION**

In our study, we focused on whether administration of octreotide could prevent the incidence of Post-ERCP pancreatitis in patients undergoing this procedure. We conducted a Prospective, single center, open labelled, a randomized placebo-controlled trial evaluating the role of prophylactic octreotide in the prevention of post-ERCP pancreatitis in Patients undergoing the procedure and whether it has any implications on the severity of post-ERCP pancreatitis.

**Post-Procedure Assessment**

In our study 7 (12.73%) patients had abdominal tenderness post procedure in the group where octreotide was administered, compared to 15 (25.86%) in the other group which is less but not statistically significant (p-value 0.07799). patients having serum amylase levels 3 times more than the upper normal limit were 3 out of the 37 patients receiving the octreotide drug in which it was done (5.45%) and 8 out of the 43 patients in the other group.

Though the incidence of hyperamylasaemia was comparatively lesser in the group that received octreotide as prophylaxis the p-value of the analysis was not significant ( $p=0.28909$ ). In the patients who underwent CT/USG for imaging to diagnose pancreatitis, none of the patients had features of acute pancreatitis while 2 patients (3.45%) in the group A had acute pancreatitis on CT scan imaging. There p value was  $>0.005$  ( $p= 0.37681$ ) suggesting no statistically significant difference in both the groups.

With any two of the above three parameters suggestive of the diagnosis (modified ATLANTA classification), we came to the final incidence of Post-ERCP pancreatitis in both the groups. In group A 2 out of 55 (3.64%) patients had Post-ERCP pancreatitis while in Group B, 6 patients out of 58 (10.34%) had pancreatitis post-ERCP. Though the incidence was less in the group which received octreotide, the p-value of the comparison between the two groups was  $>0.005$  ( $p = 0.16462$ ) and hence not statistically significant.

In our study also, we used a high-dose octreotide doses in divided doses ( $>500$  micrograms) showing a decrease in incidence but not statistically significant. The exact reason for these results with octreotide in PEP prevention remains unclear. One explanation might be as shown in the study by Testoni et al as difficult cannulation which was more frequent in the control group than in the group treated with octreotide. These findings suggest that subcutaneous injection of octreotide at least 1 hour before does not affect sphincter of Oddi contraction. The statistical insignificance of octreotide in our trial can also be attributed to the small sample study size ( $n<200$ ).

The following conditions are considered to represent a high risk for PEP: endoscopic ampullectomy, known or suspected SOD, pancreatic sphincterotomy, precut biliary sphincterotomy, pancreatic guidewire-assisted biliary cannulation, endoscopic balloon sphincteroplasty, and the presence of more than three of the risk factors listed in the table.<sup>5</sup> The ESGE guidelines have reserved the use of octreotide for high-risk patients in their updated review in 2014. Still, the need for large sample size RCTs and studies using higher doses of octreotide has been mentioned by ESGE. Hence, from our study and by reviewing the previous meta-analysis and RCTs we have the following suggestions to be made. Firstly, as seen in various studies, the incidence of PEP increases to 30% in high-risk patients. Hence, trials should be made to enrol these patients as endoscopic technique and endoscopist's experience seem insignificant risk factors in the causation of PEP. Also, the pancreatic stent is only seen to partly decrease the risk of PEP in various studies. High doses of octreotide in divided form immediately before (to reduce papillary sphincter pressure) and immediately after the procedure (to reduce pancreatic enzyme release and cause anti-inflammatory action) should be used and tested. Finally, future trials need to calculate required and sufficient sample size to reduce heterogeneity.

## CONCLUSION

From an initial era of diagnosis and therapeutics to current times where the focus lies on safer techniques and refined procedure with good clinical outcome, ERCP has changed our understanding of the various hepatobiliary and pancreatic pathologies. Hence, focusing on adverse effects and finding methods to prevent the same has been a thrust area in this field. Pharmacologic prevention of pancreatitis which is one of its most common complications has brought forward various drugs including octreotide into trials and. We conducted a prospective interventional single center randomized open placebo-controlled trial in our institute. The conclusion we reached was that though there was a decrease in the incidence of Post ERCP pancreatitis in the group receiving octreotide (in the proposed dosage form and schedule), the same was not statistically significant. Also, with the NNT value of 14.9 (relatively high) as calculated in our study, octreotide cannot be given universally in all the patients undergoing ERCP. The same needs to be used in cases of high-risk patients. As discussed by comparing other studies, there is still a need for further RCTs and subsequent meta-analysis with greater homogenous study populations and to find out dosage and schedules to administer in establishing its role in the prevention of post-ERCP pancreatitis.

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