Research Article

Risk Factors for Post Endoscopic Retrograde Cholangio Pancreatography(ERCP) Pancreatitis (PEP) and Efficacy of Octreotide in its Prevention

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Abstract

Background: Pancreatitis is a potentially fatal complication of ERCP, seen in 5-15% procedures. Factors precipitating its risk and effective pharmacological intervention for its prevention need exploration to improve patient safety.

Objective: To identify risk factors for post-ERCP pancreatitis (PEP) and to determine efficacy of intravenous octreotide in preventing PEP.

Methodology: A quasi-experimental triple blind placebo-based study included patients undergoing ERCP and randomize them in two groups through simple random sampling. Group A to receive intravenous Octreotide 4µg/kg before attempting cannulation during ERCP and 1cc N/S as placebo for group B. Patients were followed for PEP and data were analyzed using chi square (x2) and logistic regression analysis.

Results: Of 203 included patients, 101 (49.3%) received octreotide while 102 (50.7%) were in control group. Post ERCP pancreatitis developed in 32 (15.8%) patients, in 8 (7.9%) patients of octreotide group while in 24 (23.8%) patients of control group (p value 0.002 with odds ratio (OR) for octreotide of 0.33 (95% CI 0.15-0.71). We identified biliary surgery (p value 0.005), serum bilirubin ⩾ 3 mg/dl (p value 0.03), cannulation time > 5 minutes (p value <0.000), needle knife sphincterotomy (p value 0.002), deep pancreatic duct (PD) cannulation (p value <0.000) and procedure time>30 minutes (p value 0.002) as risk factors for PEP.

Conclusion: Previous biliary surgery, high serum bilirubin, cannulation time > 5 minutes, use of needle knife, PD cannulation and procedure time > 30 minutes are associated with increased risk of PEP. Intravenous octreotide before cannulation reduces risk of post ERCP pancreatitis.

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Introduction:

Acute pancreatitis is a potentially lethal abdominal emergency with annual incidence of 13-45 cases per 100000 population[1] and is associated with 20-30% risk of complications like multi-organ failure or infected necrosis with in-hospital mortality of up to 15%.[2] Diagnosis of acute pancreatitis as per revised Atlanta Classification is based on presence of 2 out of 3 parameters, (1) presence of upper abdominal pain, often radiating to back (2) serum amylase/lipase more than 3 times upper limit of normal and (3) evidence of pancreatitis on abdominal imaging study.[3]

Major causes of acute pancreatitis are gall stones and excessive ethanol intake accounting for 30-50% cases.[4]

Less common causes include hypertriglyceridemia, hypercalcemia, congenital anomalies like pancreas divisum, annulus pancreas, post Endosopic retrograde cholangiopancreaticography (ERCP) pancreatitis, autoimmune pancreatitis, trauma and drug induced pancreatitis.[5] In order to avoid recurrent episodes of pancreatitis associated with increasing risk of complications, diagnosis and treatment of underlying etiology is extremely essential.

With increasing therapeutic potential of ERCP in dealing with diseases related to biliary and pancreatic channels, post-ERCP pancreatitis (PEP) is now a major cause of iatrogenic pancreatitis. Its incidence among patients undergoing ERCP varies from 1-40%.[6] PEP results from mechanical, thermal and enzymatic injury to pancreatic duct during the procedure.[7] Why few patients are more likely to develop pancreatitis after ERCP than others is being extensively explored in centers performing this intervention. Older age, high bilirubin, difficult biliary cannulation and pancreatic duct (PD) contrast injection were identified as major risk factors for PEP in a recent study.[8] However we need better understanding of risk factors for PEP as it will help us in avoiding this post-procedure catastrophe.

Different therapeutic options are being tested for prophylaxis of PEP. Most promising results have been seen with rectal non-steroidal anti-inflammatory drugs (NSAIDs) especially indomethacin.[9] European Society of Gastrointestinal Endoscopy has recommended use of rectal NSAIDs for prophylaxis of PEP.[10] Other interventions tested are pancreatic stenting, glucagon and secretin injections, however results are far from conclusive.[11] Recently somatostatin and its synthetic analogue, octreotide have been tried for prophylaxis of PEP. Octreotide inhibits pancreatic enzyme secretion by suppressing secretin and cholecystokinin. It also exert cyto-protective effect on pancreatic cells. Bai et al in a study of 908 patients found significant benefit of somatostatin injection.[12] However studies by Consepcion Martin et al[13] and Wang et al[14] failed to identify any benefit of this therapy.

Despite being most common post-ERCP complication, risk factors for PEP are still not well defined and no pharmacological intervention has proven to be beneficial for its prophylaxis. Identification of an effective intervention to avoid PEP will remarkably improve safety and outcome of patients undergoing ERCP. Our center has published results of randomized control study of role of rectal NSAIDs therapy for prevention of PEP.[8] We planned a parallel study to determine risk factors for PEP and to determine efficacy of intravenous octreotide for prevention of PEP.

Methods

Study design was quasi-experimental, placebo based triple blind. It was conducted at Department of Medicine & Gastroenterology, Services Institute of Medical Sciences (SIMS) from June 2018 to December 2019. After approval by Internal Review Board (IRB/2018/403/SIMS: Dated 07 March 2018), Patients with uncontrolled diabetes mellitus, abnormal thyroid functions, diagnosed ischemic heart disease or on-treatment for cardiac arrhythmias were excluded. Patients with history of pancreatitis in last 4 weeks, antibiotics or NSAIDs use in last 2 weeks and those pregnant or breast feeding were also not enrolled. Study sample size needed to achieve at least 50% reduction in PEP with octreotide as compared to no treatment as calculated online with EPITOOL® was 196 with desired power of 80%, confidence interval of 95% while keeping margin of error < 5%.

Detailed clinical history and examination followed by review of medical record was carried out for each patient. Results of routine laboratory tests and radiological investigations including ultrasound, CT scan, MRI or MRCP were recorded. Using online random table generator stat trek®, patients were randomized in two groups, Group A(n=101) received intravenous Octreotide 4 µg/kg during procedure before attempting cannulation whereas Group B(n=102) received 1cc of 0.9% normal saline as placebo during ERCP. Identity of patient's group was only known to one investigator (AA) whereas patient, endoscopist and doctor responsible for follow up after ERCP were blinded to treatment group identity.

Two senior consultants (MAN and SS) performed all ERCP procedures under Propofol sedation. Sedation was monitored by dedicated nursing assistant. Time to wire guided cannulation, needle knife use, deep pancreatic duct cannulation or contrast injection in pancreatic duct, sphincterotomy, biliary dilatation, stone extraction, biliary or pancreatic duct stenting and total procedure time were the variables recorded during procedure.

Post procedure, patient was shifted and monitored in

recovery room for minimum of 24 hours by senior consultant (SS) unaware of patient's group of treatment. Serum amylase was checked after 6 hours of ERCP and more than 3 fold increase with typical abdominal pain was diagnosed as acute pancreatitis as per Atlanta criteria.[3] Post-ERCP pancreatitis was treated as per standard management plan while those free of symptoms were discharged.

Efficacy of octreotide was considered significant if it reduced incidence of post ERCP pancreatitis by at least 50% as compared to control group.

Results:

Data were analyzed using SPSS 22® (Armonk NY: IBM® corp) without disclosing identity of group A and B.

Quantitative variables with normal distribution were given as mean± standard deviation (SD) while nonparametric variables were described as median ±. interquartile range (IQR). Percentage was used for qualitative variables. Outcome variables between two groups were compared using unpaired student's t test and chi square (x^2) test to determine Odd's ratio (OR).

Variables with significant association with PEP on univariate analysis had multi-variate binary logistic regression analysis using post-ERCP pancreatitis as dependent variable.

We included 203 patients in study. Mean age of patients included was 49.3 (±15.4) years with male to female ratio of 1:1.38 (85/118). Major presenting complaint among study patients was abdominal pain in 165 (81.3%) patients followed by jaundice in 127(62.6%), fever in 105(51.7%) and pruritus in 89 (43.8%) patients. Past history of pancreatitis was present in 20(9.9%) patients while 35 (17.2%) had prior cholecystectomy. ERCP was being repeated in 38 (18.7%) patients.

Common bile duct (CBD) stone was indication for ERCP in 108 (53.2%) patients, 33 (16.3%) patients had pancreatic carcinoma, 23 (11.3%) had cholangiocarcinoma, 15(7.4%) had ERCP for biliary leakage following cholecystectomy and 10 (5.1%) had benign biliary stricture. Recurrent pancreatitis 5(2.5%), gall bladder tumor 3(1.5%), peri-ampullary mass 4(2%), choledochal cyst 1(0.5%) and pancreatic stone 1(0.5%) were other indications for ERCP. After randomization 101(49.7%) received octreotide for PEP prophylaxis while 102 (50.3%) patients were in control group receiving 0.9% N/S as placebo. Both groups were comparable in baseline characteristics as shown in table-1.

Table 1: *Comparison of group A and group B*

Variable	Group A (Octreotide) (n-101) Mean ± SD	Group B (Placebo) (n-102) Mean ± SD	P value
Age (Years)	48.5 ± (14.8)	50.2 ± (15.9)	0.43
Bilirubin (mg/dl)	5.57 ± (7.4)^	7.17 ± (9.3)^	0.17 *
Creatinine (mg/dl)	0.88± (0.9)	0.88 ± (0.2)	0.99
Procedure time (min)	37.8 ± (12.0)	32.4 ± (15.5)	0.007
	No of patients	No of patients	
Gender (M/F)	41/60	44/58	0.71
H/o previous pancreatitis	8	12	0.35
H/O surgery	18	17	0.82
H/O previous ERCP	23	15	0.14
Dilated CBD	34	34	0.96
CBD stones	52	56	0.62
Pre-cut sphincterotomy	16	16	0.97

SD: Standard deviation
^: Interquartile range (IQR)
*: Mann Whitney U test

During ERCP, cannulation was achieved in less than 5 minutes in 107 (52.7%) patients while needle knife was needed for cannulation in 32(15.8%) patients. Deep pancreatic duct (PD) cannulation was done in 52(25.6%) cases while PD was injected with contrast in 20 (9.9%) patients. Sphincterotomy was performed in 159 (78.3%) patients, stones were extracted in 95(46.8%) patients, 88(43.3%) had CBD stenting and 4 (2%) patients had PD stenting. Total procedure time was more than 30 minutes in 115 (56.7%) patients.

Post ERCP, 90 (44.3%) patients developed abdominal pain however pancreatitis was diagnosed in 32 (15.8%) patients while 14 (6.9%) patients had serum amylase >3 times normal with no symptoms. All patients with PEP recovered and were discharged with no complication. PEP was diagnosed in 24 (23.5%) patients of placebo group as compared to 8 (7.9%) patients in octreotide group, significantly less with octreotide therapy (p value 0.002) with odds ratio (OR) of 0.33 (95% CI 0.15-0.71). With more than 50% reduction in PEP, Octreotide use was effective in reducing PEP.

We analyzed various patient and procedure related variables for increasing the risk of PEP and identified

previous history of biliary surgery, OR 2.51(95% CI 1.33-4.7) (p value 0.005), serum bilirubin ⩾ 3 mg/dl, OR 1.97 (95% CI1.01-3.8) (p value 0.03), cannulation time > 5 minutes, OR 3.88 (95% CI 1.67-9.04) (p value <0.000), needle knife sphincterotomy OR 2.79 (95% CI 1.49-5.22) (p value 0.002), deep PD cannulation OR 3.29 (95% CI 1.77-6.11) (p value <0.000) and procedure time>30 minutes OR 3.31 (95% CI 1.42-7.7) (p value 0.002) to be significantly associated with post-ERCP pancreatitis on uni-variate analysis.

On multi-variate binary regression analysis, model comprising of these 6 variables with significant association with PEP, showed 86.2% accuracy in predicting post-ERCP pancreatitis with 2 log likelihood of 139.09 as shown in table-2. P value of 0.30 of Hosmer and Lemeshow test favors excellent correlation between model-based expected outcome and observed outcome of PEP. History of previous surgery (p value 0.002) and deep pancreatic duct cannulation (p value 0.03) stood the rigor of multi-variate analysis in predicting PEP. (Table-3).

Table 2: *Accuracy of Model in predicting PEP*

Observed			Predicted		
			Clinical pancreatitis		Percentage Correct
			No	Yes	
Step 1	Clinical pancreatitis	No	164	7	95.9
		Yes	21	11	34.4
	Overall Percentage				86.2

a. The cut value is .500

along with different prophylactic options to prevent PEP, incidence of post-ERCP pancreatitis has remained unchanged in last few decades. Identification of risk factors for PEP will enable us to focus prophylactic interventions on high risk patient group to reduce its incidence. However with introduction of sophisticated interventions during ERCP like choledochoscopy, electro-hydraulic lithotripsy and use of endoscopic ultrasound for difficult cannulations, risk stratification for PEP is an evolving field.

In a study of 1786 patients by Guo-Zhen Li et al, deep pancreatic cannulation, post-liver transplantation ERCP and metallic biliary prosthesis were associated with high risk of PEP.[15] Deep wire pass in pancreatic duct results in pancreatic duct injury leading to initiation of cascade of inflammation culminating in pancreatitis.[16] Needle knife precut sphincterotomy was identified to be an independent risk factor for PEP in a meta-analysis.[17] Among different techniques of precut like fistulotomy, transpancreatic precut or needle knife precut, fistulotomy has highest risk of PEP.[18] Wang J et al concluded that difficult intubation, pancreatic duct intubation, longer duration of procedure and previous history of pancreatitis increases risk of PEP.[19]

European Society of Gastrointestinal Endoscopy (ESGE) has identified cannulation time more than 10 minutes, pancreatic guidewire passages more than 1 time and pancreatic injection as definitive risk factors while precut

Table 3: *Multivariate binary regression analysis*

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1[a]	HOS	1.604	.528	9.232	1	.002	4.974	1.767	14.000
	BIL3	.797	.466	2.925	1	.087	2.220	.890	5.535
	TC5	.943	.560	2.840	1	.092	2.568	.858	7.688
	precut	.937	.517	3.277	1	.070	2.551	.925	7.034
	PDC	.959	.456	4.419	1	.036	2.609	1.067	6.381
	TP30	.659	.553	1.423	1	.233	1.933	.654	5.709
	Constant	-9.993	1.693	34.852	1	.000	.000		

a. Variable(s) entered on step 1: HOS, BIL3, TC5, precut, PDC, TP30.

HOS: History of surgery
BIL3: Bilirubin value 3 mg/dl or more
TC5: Time to cannulation more than 5 minutes
Precut: Precut done
PDC: Pancreatic duct cannulation
TP30: Total procedure time more than 30 minutes

Discussion:

Despite all the advances in techniques and equipment sphincterotomy, biliary balloon dilatation, pancreatic sphincterotomy and failure to clear bile duct stones as likely risk factors for PEP.[20] We identified previous

history of biliary surgery, bilirubin of 3 mg/dl or higher, cannulation time more than 5 minutes, pancreatic duct cannulation, use of precut sphincterotomy and procedure time more than 30 minutes as risk factors for PEP. These are the patients where we need to use prophylactic interventions to prevent PEP.

We used intravenous Octreotide 4 µg/kg before cannulation during ERCP for prophylaxis of PEP, it resulted in significant reduction in incidence of PEP, from 23.5% in control group to 7.9% in patients receiving medication. Octreotide, a somatostatin analogue inhibits pancreatic exocrine function directly by inhibiting secretions and indirectly by controlling secretin and cholecystokinin.[21] Bai et al tested I/V octreotide 250 µg before procedure and 250 µg/hr for 11 hours after ERCP, PEP reduced from 7.5% in control group to 4% in treatment arm.[12] Concepcion-Martin et al used 4 hours infusion of Octreotide[13] while Wang et al used 0.5 mg/hr infusion starting 1 hour before procedure till 24 hours after ERCP.[14] Both studies failed to show any benefit of using Octreotide infusion in preventing PEP. In a study of 151 patients, Arcidiacono et al used subcutaneous Octreotide 0.1 mg, 120 minutes, 30 minutes before and 4 hours after procedure, despite no difference in PEP as compared to control group, earlier improvement in serum amylase level and lesser severity of PEP was noted with octreotide.[22]

In order to improve therapeutic outcome, Wang Jin et al combined I/V infusion of 0.3 mg Octreotide starting 1 hour before till 24 hours after ERCP with rectal Indomethacin half hour before procedure, it reduced PEP from 20.8% to 5.97%.[19] Similarly Katsinelos et al in a double blind randomized study of 540 patients, used I/V Somatostatin along with Diclofenac suppository of 100mg for prevention of PEP and noted decline in PEP from 10.4% in control group to 4.7% in treated patients which was statistically significant.[23] As post-ERCP pancreatitis is a potentially fatal post-procedure complication and if results of monotherapy for its prophylaxis continue to be equivocal, combination therapy can be the ultimate solution for prophylaxis, however data is far from conclusive.

Incidence of PEP in our study was 15.8% in our study which is on higher side when compared to international literature, especially 23.5% in control group. However both groups were comparable when confounding variables like age, gender, indication for procedure and comorbid issues are considered. Our study was conducted in single center where only patients being admitted or referred to our center for ERCP were included. A multicenter study with more diverse group of patients being tested for efficacy of octreotide for prophylaxis of PEP will augment evidence for efficacy and safety of this drug.

We have shown efficacy of single dose of octreotide before ERCP whereas previously its infusion over hours to days has been studied. It can improve the convenience of medication, improving compliance along with avoidance of need for longer post procedure hospital stay and monitoring of patient. Further data regarding single dose Octreotide before ERCP at multiple centers and may be in combination with other drugs like NSAIDs can help in identifying efficient primary prophylaxis of PEP.

Conclusion:

Previous biliary surgery, high serum bilirubin, cannulation time > 5 minutes, use of needle knife, deep PD cannulation and procedure time > 30 minutes are associated with increased risk of PEP. Intravenous octreotide before cannulation during ERCP reduces risk of PEP.

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