

# Role of N-acetyl cysteine for the prevention of post-endoscopic retrograde cholangio-pancreatography pancreatitis

Hossain RMM<sup>a</sup>, Bhuiyan TM<sup>b</sup>, Azam MG<sup>c</sup>, Datta IK<sup>c</sup>, Al-Mamoon MA<sup>c</sup>

## ABSTRACT

**Background:** Pancreatitis is one of the common complications of endoscopic retrograde cholangio-pancreatography (ERCP) procedure. Pathogenesis of acute pancreatitis is probably the capillary endothelial injury mediated by oxygen-derived free radicals. Different medications and procedures have been used to prevent post-ERCP pancreatitis (PEP) but are of little benefit. N-acetyl cysteine (NAC) is a safe free radical scavenger. The aim of this study was to evaluate prevention of PEP by inhibiting inflammatory intermediates and oxidative stress with NAC.

**Methods:** This quasi-experimental study was carried out at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD) of BIRDEM General Hospital, Dhaka, Bangladesh from January 2018 to July 2019. After meeting the eligibility criteria, total 150 candidates for ERCP were enrolled in this study. Patient lists were collected from ERCP procedure room and patients with uneven serial numbers were selected into the N-group who received a colorless solution of 1200 mg NAC (1200 NAC dissolved with 150 cc water) orally 2 h before ERCP and patients with even serial numbers were selected into the P-group who received only 150 cc water. Serum lipase was measured 2 times: at 4 hours and 24 hours after ERCP. Patients who developed PEP were also evaluated for the risk factors of PEP.

**Results:** PEP occurred in 34 patients (22.6%) out of 150 study subjects [mild 20 (13.3%), moderate 13 (8.6%) and severe 1 (0.7%)]. From N-group 17 patients (22.6%) and from P-group 17 patients (22.6%) developed PEP (*p* value 0.577). Risk factor analysis revealed that the young age group, patients with type-2 diabetes (T2DM) getting insulin, difficult cannulations, injection of contrast into the pancreatic duct and trainee involvement in the procedure were statistically significant. In multivariate analysis, the young age group, patients with T2DM getting insulin and trainee involvement remained the risk factors of PEP.

**Conclusion:** In conclusion, N-acetyl cysteine had no role in the prevention of PEP in this study.

**Key words:** N-acetyl cysteine, post-endoscopic retrograde cholangio-pancreatography, pancreatitis.

*BIRDEM Med J 2023; 13(1): 38-43*

## Author information

- Riad Mohammad Moshaed Hossain, Senior Medical Officer, Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Dhaka, Bangladesh
- Tareq M Bhuiyan, Professor and Head, Department of GHPD, BIRDEM General Hospital, Dhaka, Bangladesh.
- Mohammad Golam Azam, Indrajit Kumar Datta, Md. Abdullah Al Mamoon, Associate Professor, Department of GHPD, BIRDEM General Hospital, Dhaka, Bangladesh.

**Address of correspondence:** Riad Mohammad Moshaed Hossain, Senior Medical Officer, Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Dhaka, Bangladesh. Email: drhossain1977@gmail.com

**Received:** July 25, 2022

**Revision received:** November 5, 2022

**Accepted:** December 13, 2022

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most complex endoscopic procedures performed with a side view scope. It is widely used as a therapeutic modality for benign and malignant diseases involving the pancreato-biliary tree.<sup>1</sup> The reported incidence of ERCP-specific complications ranges from 5 to 40%, depending on the complexity of the procedure, the underlying diagnosis and comorbidities associated with patients.<sup>2-3</sup> Acute pancreatitis remains the most common and serious complication after ERCP with a reported incidence ranging from 1.3 to 15.1% resulting in substantial morbidity and occasional mortality.<sup>4-10</sup> Rather than having single pathogenesis, post-ERCP pancreatitis

(PEP) is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, microbiologic, and thermal factors.<sup>10</sup> More than 35 pharmacologic agents have been studied in many prospective clinical trials to prevent PEP, but no medication has been proven to be consistently effective.<sup>11</sup> N-acetyl cysteine (NAC) as an antioxidant could prevent pancreatitis by inhibiting inflammatory intermediates and oxidative stress.<sup>12,13</sup> Several studies have been conducted to establish the role of NAC to prevent post ERCP pancreatitis.<sup>14,15</sup> Only a few studies showed NAC significantly prevents PEP including the study done at Ahwaz Imam Hospital in 2013.<sup>14</sup> It would be due to the different pharmacokinetics of NAC followed in different studies. The aim of this study was to evaluate prevention of PEP by inhibiting inflammatory intermediates and oxidative stress with NAC.

## METHODS

This was a quasi-experimental study. This study was carried out at the Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD) Department of BIRDEM General Hospital, Dhaka, Bangladesh, from January 2018 to July 2019. Patients who were selected for ERCP were evaluated with eligibility criteria (no H/O allergy / hypersensitivity to N-acetyl Cysteine, not received NSAIDS in prior 7 days, not known as chronic pancreatitis). Total 150 subjects were enrolled in this study. Patient lists were collected from ERCP procedure room and patients with uneven serial numbers were selected into the N-group who received a colorless solution of 1200 mg NAC (1200 NAC dissolved with 150cc water) orally 2 h before ERCP. And patients with even serial numbers were selected into the P-group who received only 150cc water. Patients were kept under surveillance in the endoscopy recovery area for 24 hours after ERCP. Serum lipase was measured 2 times: at 4 hours, and 24 hours after ERCP. ERCP procedures were carried out by both experts and trainee doctors. Patients who developed abdominal pain during this observation period were generally kept in the hospital to exclude procedural complications, including pancreatitis and perforation. Patients who developed PEP were also evaluated for the risk factors of PEP. Patient demographics, biochemical parameters, risk factors, the procedural elements of the ERCP, and follow-up data

was recorded on a standardized data collection form (appendix A) at the time of the procedure, 4 hours after the procedure and 24 hours after the procedure. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows. Various tests of significance were done where applicable to compare data and  $p < 0.05$  was used as the minimum level of significance.

## Operational definitions

### Post ERCP pancreatitis

Post-ERCP pancreatitis, was defined according to consensus criteria:<sup>16</sup>

- 1) New or worsened abdominal pain that is clinically consistent with pancreatitis and
- 2) Lipase  $e''$  3x the upper limit of normal at 24 hours after the procedure and
- 3) Hospitalization (or prolongation of existing hospitalization) for at least 2 days (at least night of ERCP and next night).

### Severity of pancreatitis

Mild: Mild PEP was defined as pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for  $d''3$  days.

Moderate: Moderate PEP was defined as pancreatitis that results in hospitalization for 4-10 days.

Severe: Severe PEP was defined as pancreatitis that results in hospitalization for  $> 10$  days

### Difficulty of cannulation

It was determined on the basis of the number of attempts on the major papilla with a cannulation instrument before final: easy (one to five attempts); moderate (six to 15 attempts); and difficult ( $> 15$  attempts)<sup>16</sup>.

### Ethical implication

Ethical permission from institutional review board was taken. Written informed consent was taken from each patient.

## RESULTS

Of the enrolled 150 patients, 75 were into the N group and 75 into the P group. The demographic characteristics of patients are shown in Table I.

**Table I.** Comparison of demographic characteristics of the study population among two groups (N=150)

Characteristics	Group		p-value
	N(n=75)	P(n=75)	
Male (n %)	43(57.3)	28(37.3)	0.292
Female (n %)	32(42.6)	47(62.6)	
Age (Year)mean±SD	54.91±10.68	55.21±13.82	0.879
Smoker (n %)	37(49.3)	26(34.6)	0.521
Alcoholic (n %)	1(1.3)	2(2.6)	0.689
Regular tea/coffee user(n %)	33(44.0)	29(38.6)	0.580
Diabetic (n %)	53(70.6)	48(64.0)	0.359
On insulin	40(75.4)	34(70.8)	0.207

Data were expressed as n (%)  
Chi-square test was done to measure the significant difference among the groups

After ERCP commonest diagnosis was choledocholithiasis. Other diagnoses are showed in Table II.

**Table II.** Distribution of patients according to post ERCP diagnosis between two groups (n=150)

Post ERCP diagnosis	Group	
	P(n=75)	N(n=75)
Choledocholithiasis	39(52.0)	34(56.7)
SuspectedSOD	14(18.6)	13(17.3)
Peri-ampullary carcinoma	8(10.0)	11(3.3)
Cholangio-carcinoma	8(10.6)	12(16.0)
Carcinoma GB involving biliary tree	2(2.6)	1(6.7)
Other	4(5.3)	4(5.3)

Data were expressed as n (%)  
SOD: Sphincter of Oddi dysfunction  
GB: Gall bladder

In this study, 34 patients (22.6%) developed PEP out of 150 ERCP procedures and 17 cases in each group. The difference was not significant. (p 0.577); Table III.

**Table III.** Distribution of patients according to post ERCP pancreatitis (PEP) between two groups (N=150)

PEP	Group		p-value
	N (n=75)	P(n=75)	
Yes	17(22.6)	17(22.6)	
No	58(77.3)	58(77.3)	0.577
Total	75(100.0)	75(100.0)	

Data were expressed as n (%)  
Chi-square test was done to measure the significant difference among groups

Mild cases were more common in the N group (N 64.7% vs P 52.94%) and moderate cases are in the P group (N 35.3% vs P 41.17%) but there was no significant difference between the two groups (p 0.499). (Table IV)

**Table IV.** Distribution of patients according to severity of post ERCP pancreatitis between two groups (n=34)

PEP	Group		p-value
	N (n=19)	P (n=20)	
Mild	11(64.7)	9(52.9)	
Moderate	6(35.3)	7(41.1)	0.499
Severe	0(0.0)	1(5.8)	
Total	17(100.0)	17(100.0)	

Data were expressed as n (%)  
Kruskall Walli's test was done to measure the significant difference among three groups.

Regarding the risk factors for PEP, the young age group, patient of T2DM getting insulin, difficult cannulations, injection of contrast into the pancreatic duct and trainee involvement in the procedure are significant.

**Table V.** Risk factors for the development of PEP between two groups (N=150)

Risk factors	Group		p-value
	PEP	No-PEP	
<b>Patient related risk factors</b>			
Young age (<50years)	05	36	0.044
Female gender	19	65	0.570
Diabetes	26	75	0.139
On insulin	24	52	0.007
High alkaline phosphatase	27	95	0.458
Normal serum bilirubin level	13	43	0.527
Suspected SOD	08	21	0.316
Prior ERCP-induced pancreatitis	01	02	0.540
<b>Procedure related risk factors</b>			
Difficult cannulation	11	18	0.030
Needle papillotomy	28	85	0.198
Pancreatic duct injection	08	10	0.025
Pancreatic sphincterotomy	01	03	0.647
Trainee involvement in procedure	04	02	0.024

Chi-square test was done to measure the significant difference among groups

The logistic regression analysis reveals, the young age group, patients with T2DM getting insulin, and trainee involvement are the significant risk factors of PEP. (Table VI).

**Table VI.** Multiple logistic-regression analysis of variables with development of PEP

Variables	Odds ratio	95% C.I.		p-value
		Lower	Upper	
Young age	1.973	0.672	5.789	0.216
On Insulin	0.415	0.175	0.988	<b>0.047</b>
Difficult cannulation	0.526	0.177	1.560	0.247
Pancreatic duct inj.	0.382	0.108	1.361	0.138
Trainee involvement	0.141	0.023	0.866	<b>0.034</b>

## DISCUSSION

Although several technical and patient-related risk factors for PEP have been identified, the knowledge of risk factors is often not helpful in the prevention of pancreatitis. For these reasons, several trials had been conducted with different pre-procedural measures to prevent PEP.

A study was done at Ahwaz Imam Hospital in 2013 showed,<sup>14</sup> that NAC significantly prevents PEP (risk reduction ratio: 2.8; p=0.02).<sup>22</sup> But in this study, N-acetyl cysteine demonstrated no role in the prevention of PEP. Our results are consistent with the study by Janusz Milewski et al.<sup>15</sup> These patients were randomized into two groups. In the treated group, two 600 mg doses were given orally 24 h and 12 h before ERCP and 600 mg was given intravenously, twice a day for two days after the ERCP. The control group was given intravenous isotonic saline twice a day for two days after the ERCP. There were no significant differences in the rate of PEP between the two groups.

Up to now, routine prophylaxis has not been adopted in the majority of centers that conduct ERCP procedures or are recommended in guidelines. However, the procedure or patient-related risk factors vary widely from study to study and these discrepancies may be due to differences in patient populations, indications, endoscopic techniques, endoscopic expertise, methods of data collection and the use of preventive techniques such as placement of pancreatic stents<sup>18-20</sup>.

Younger age was associated with a high risk for pancreatitis in the multivariate analysis and there was an inverse relationship between age and the occurrence of PEP. Younger age was first identified as an independent risk factor for PEP in a multicenter study in 1964 and subsequently confirmed in four other multivariate analyses<sup>21-24</sup>. The higher risk may be explained by the progressive decline in pancreatic exocrine function with aging that may protect older patients from pancreatic injury<sup>14</sup>.

Insulin resistance is the hallmark of DM.<sup>25</sup> Seung Kook Cho demonstrated that insulin resistance assessed using Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was significantly associated with severity of pancreatitis and Intensive Care Unit admission.<sup>25</sup> Ali Riza Koksali et al. found insulin levels were statistically significantly higher in patients who

developed PEP than in the ones who did not.<sup>26</sup> This current study reveals, PEP is significantly more in people with DM getting insulin than in people without insulin (p value 0.046).

In the multivariate analysis of a randomized controlled multicenter study by Cheng et al<sup>16</sup> revealed trainee involvement in the procedure was found to be a risk factor for the development of PEP and this study showed similar result.

### Conclusion

According to this study, N-acetyl cysteine has no role in the prevention of PEP, hence, more studies with N-acetyl cysteine using different doses and routes are still needed. And further studies should be on large scale and multi-center.

**Authors' contribution:** RMMH, TMB, MGA conceived idea of research. RMMH drafted manuscript. All authors submit for publication.

**Conflicts of interest:** Nothing to declare

### REFERENCES

- Baron T H, Kozarek R, Carr- Locke D L. ERCP.1st ed. Saunders Elsevier: 2008. P 52.
- Vandervoort J, Soetikno RM, Tham TC, Wong RC, Montes H, Roston AD, et al. Risk factors for complications after performance of ERCP. *Gastrointest Endosc* 2002; 56: 652–6.
- Jaik NP, Hoey BA, Stawicki SP. Evolving role of endoscopic retrograde cholangiopancreatography in management of extrahepatic ductal injuries due to blunt trauma: diagnostic and treatment algorithms. *HPB Surg* 2008; 2: 59-141.
- Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Moore JP, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med*:1996;335:909-18.
- Loperù do S, Angelini G, Benedetti G, Costan F, Ederle A, Fina P, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *GastrointestEndosc* 1998; 48: 1– 10.
- Freeman ML, DiSario JA, Nelson DB, Lee J G, Ryan ME, Shaw MJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *GastrointestEndosc* 2001; 54: 425–34.
- Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; 96: 417–23.
- Freeman M, DiSario JA, Nelson DB, Fennerty MB. Risk factors for pancreatitis after diagnostic and therapeutic ERCP [abstract]. *GastrointestEndosc* 1996; 43: AB400.
- Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; 39: 793 –801.
- Gottlieb K, Sherman S. ERCP and biliary endoscopic sphincterotomy-induced pancreatitis. *Gastrointest Endosc Clin N Am* 1998; 8: 87–114.
- Cha SW , Leung WD, Lehman GA, Watkins JL, McHenry L, Fogel EL, et al. Does leaving a main pancreatic duct stent in place reduce the incidence of precut biliary sphincterotomy-associated pancreatitis? A randomized, prospective study. *GastrointestEndosc* 2013; 77: 209–216.
- Katsinelos P, Kountouras J, Paroutoglou G, Beltsis A, Mimidis K, Zavos C. Intravenous N-acetylcysteine does not prevent post-ERCP pancreatitis. *Gastrointest Endosc* 2005;62:105-11.
- Milewski J, Rydzewska G, Degowska M, Kierzkiewicz M, Rydzewski A. N-acetylcysteine does not prevent postendoscopic retrograde cholangiopancreatography hyperamylasemia and acute pancreatitis. *World J Gastroenterol* 2006;12:3751-5.
- AlaviNejad P, Hajiani E, Hashemi J, Masjedizadeh AR, Shayesteh AA, Sebghatollahi V. Evaluation of N-acetyl Cysteine for the Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Prospective Double-Blind Randomized Pilot Study. *Middle East J Dig Dis.* 2013, 5:17-21.
- Nonaka A, Manabe T, Tobe T. Effect of a new synthetic ascorbic acid derivative as a free radical scavenger on the development of acute pancreatitis in mice. *Gut* 1991; 32: 528-32.
- Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; 101: 139–47.
- Shi C, Zhao X, Lagergren A, Sigvardsson M, Wang X, Andersson R. Immune status and inflammatory response differ locally and systemically in severe acute pancreatitis. *Scand J Gastroenterol* 2006;41:472-80.
- Cotton PB, Garrow DA, Gallagher J, Joseph R. Risk factors for complications after ERCP: a multivariate analysis of 11497 procedures over 12 years. *GastrointestEndosc* 2009; 70: 80–8.
- Dickinson RJ, Davies S Post-ERCP pancreatitis and hyperamylasemia: the role of operative and patient factors. *Eur J GastroenterolHepatol* 1998; 10: 423–8.

20. Bakman YG, Safdar K, Freeman ML. Significant clinical implications of prophylactic pancreatic stent placement in previously normal pancreatic ducts. *Endoscopy* 2009; 41:1095-8.
21. DiMagno MJ, Spaete JP, Ballard DD, Wamsteker EJ, Saini SD. Risk models for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP): smoking and chronic liver disease are predictors of protection against PEP. *Pancreas* 2013; 42: 996-1003.
22. Mazaki T, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. *J Gastroenterol* 2013 Apr 24; Epubaheadof print [PMID: 23612857 DOI: 10.1007/s00535 -013-0806-1]
23. Mehta SN, Pavone E, Barkun JS, Bouchard S, Barkun AN. Predictors of post-ERCP complications in patients with suspected choledocholithiasis. *Endoscopy* 1998; 30: 457-63.
24. Sherman S, Lehman GA, Freeman ML, Earle D, Barnett J, Johanson J, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study [abstract]. *Am J Gastroenterol* 1997; 92: 1639.
25. Cho SK, Huh JH, SaeYoo J, Kim, Lee KJ. HOMA-estimated insulin resistance as an independent prognostic factor in patients with acute pancreatitis *Scientific Reports |* (2019) 9:14894
26. Koksai AR, Boga S, Alkim H, Bayram M, Ergun M, Alkim C. Insulin Resistance as a Novel Risk Factor for Post-ERCP Pancreatitis: A Pilot Study DOI 10.1007/s10620-016-4127-0