Evaluation of N-acetyl Cysteine for the Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Prospective Double Blind Randomized Pilot Study

Pezhman Alavi Nejad[1,2*], Eskandar Hajiani[1,2], Jalal Hashemi[1,2], Abdol Rahim Masjedizadeh[1,2], Ali Akbar Shayesteh[1,2], Vahid Sebghatollahi[2]

1. Research Institute for Infectious Diseases of the Digestive System, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahwaz, Iran

* **Corresponding Author:**
Pezhman Alavi Nejad, MD
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Ahvaz Jundishapur University of Medical Sciences, Imam Hospital, P.O. Box 89, Ahvaz, Iran
Telefax: + 98 611 2921839
Email: Pezhmanalavinejad@gmail.com
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ABSTRACT

BACKGROUND

Acute pancreatitis is the most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP) that can occasionally be fatal. Multiple drugs have been examined for the prevention of this side effect, with generally uncertain results. This study is an effort to prevent this complication by the use of oral N-acetyl cysteine (NAC).

METHODS

A total of 100 patients who were candidates for ERCP were divided randomly into two groups. In the NAC (N) group, patients received 1200 mg NAC with 150 cc water orally 2 h before ERCP. In the placebo (P) group, 150 cc water was prescribed as a placebo. We measured serum amylase and lipase levels before and 24 h after ERCP. The prevalence of pancreatitis and duration of admission in each group were determined and compared.

RESULTS

In group N there were 5 (10%) cases of pancreatitis, whereas in group P there were 14 (28%) cases, which was significant (risk reduction ratio: 2.8; p=0.02).The average admission time was 1.16±0.55 days in group N and 1.18±0.44 days in group P, which was not significant.

CONCLUSION

There were significant differences in the prevalence of acute pancreatitis between the two groups. In addition, the number of need to treat (NNT) consisted of five cases for NAC. With regards to the above results and the safety profile of NAC, it could be used as a therapeutic agent for the prevention of post-ERCP pancreatitis. We recommend that the results of this study be verified by additional clinical trials.

KEYWORDS

Pancreatitis; ERCP; N-acetyl Cysteine; Amylase; Lipase

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure performed with a side view scope that can be either diagnostic or therapeutic.[1] 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% (average: 5%).[1-5] Pancreatitis was responsible for more than half of the major side effects in two large case series,[4,6] and in some cases it has been fatal.[3,4,6]

An increase in serum amylase levels following ERCP is common, occurring in approximately 75% of patients. Clinically acute pancreatitis, which is defined as abdominal pain and an increase in serum amylase levels greater than 260 U, has been seen in 5% to 7% of patients. In some groups, such as sphincter of Oddi dysfunction (SOD) which is a benign non-calculus obstructive disorder that occurs at the level of the sphincter of Oddi,[7] there have been reports of acute pancreatitis in as many as 25% of patients.[2,3,6] Pancreatitis is the most important side effect of ERCP, therefore discovering a way to prevent it is reasonable.

Probable mechanisms for inducing pancreatitis after ERCP are mechanical, hydrostatic, chemical, microbiologic, thermal, and enzymatic;[2,6] although the relative role of each has yet to be determined.[4-6] Different medications have been used as therapeutic interventions for the prevention of this side effect, but are of little benefit.[8-17] These medications include octreotide, somatostatin, gabexate mesylate, corticosteroids, heparin, allopurinol, and anti-histamines.

One hypothesis involves the role of active oxygen and nitrogen compounds and oxidative stress in the pathogenesis of pancreatitis,[5] of which these compounds activate an inflammatory cascade and immune responses. According to this theory, N-acetyl cysteine (NAC) as an anti-oxidant agent could prevent pancreatitis by inhibiting inflammatory intermediates and oxidative stress. Although experiments with the intravenous form of this drug have been unsuccessful,[10,18] one study from Sweden in 2006 has shown that oral NAC could reduce the concentration of NF-kB in pancreatic ducts and decrease the severity of pancreatitis.[10] No clinical trials have evaluated the clinical benefits of this medication, as based upon the results of this study. If the low price, safety profile, and negligible adverse effects of this drug prove to be beneficial in clinical trials, it can be used as an effective therapy for the prevention of pancreatitis. Thus this study has been designed to evaluate oral NAC in the clinical practice, with the intent to prevent post-ERCP pancreatitis.

MATERIALS AND METHODS

In this study all patients who were candidates for ERCP at Ahwaz Imam Hospital that met the inclusion criteria and had no contraindications for participating in the study were included. Exclusion criteria included the presence of uncontrolled diabetes mellitus, established pancreatitis before ECRP, unwillingness to undergo ERCP, serum Triglyceride>1000 mg/dl, and anatomical changes to the stomach from previous surgeries. We randomly divided the patients into two groups, NAC (N) and placebo (P). Randomization was performed by computer.

We designed an algorithm for this RCT (Figure 1). Before performing ERCP, baseline serum amylase and lipase levels were obtained from all patients. The medication was prepared by dissolving 1200 mg of NAC in 150 cc water. All patients in the N group received NAC as an oral medication. The P group received 150 cc of water. Patients took either the medication or placebo 2 h before ERCP. At 24 h after ERCP, patients' serum amylase and lipase levels were measured. Additionally, patients were examined for abdominal pain. The duration of the hospital stay was recorded. All ERCP procedures were performed by gastroenterologists and we recorded the average time for performing the procedure and the mean volume of contrast agent used for comparison between the two groups. The recorded data was retained for final analysis.

The normal upper limits of amylase and lipase are defined as <65 U/ml in a reference kit. Pancreatitis is defined as serum amylase levels >275 U/ml or serum lipase levels >1000 U/ml with the presence of abdominal pain.[7] We have defined the severity of pancreatitis based on the number of hospitalized days following ERCP as mild (<4 days), moderate (4 to 10 days), or severe (>10 days) and compared the results from both groups. This was a

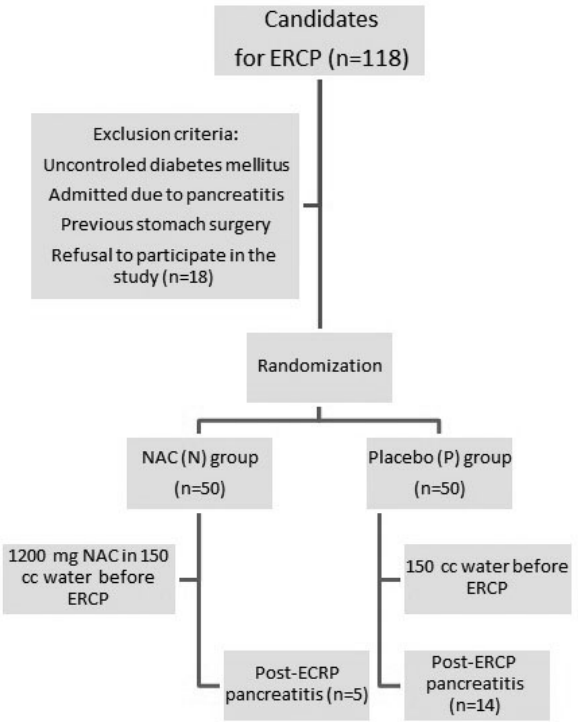

Fig. 1:The study algorithm.

double blind study; neither the patient nor ERCP technician was informed about the treatment assignment. During the study we managed and recorded the presence of any ECRP-related adverse events, including hemorrhage, perforation, and cholangitis.

Blood sampling was performed by the staff of the gastroenterology ward and the serum samples were sent to one standard laboratory and measured by one kit. This study was a pilot study that enrolled 100 patients randomly divided into an intervention (n=50) group and a placebo (n=50) group.

For interpretation and data analysis, the variables were first determined and defined by statistical methods (tables and charts). To determine the relation between quantitative and qualitative variables we used the t- and Chi-2 tests. *P*-values less than 0.05 were considered significant. Data were analyzed by SPSS version 16 software. The primary outcome of this study was to decrease the rate of post-ERCP pancreatitis. The secondary outcomes included decreasing the duration of hospitalization and prevention of morbidity and mortality. A description of the study and potential hazards were given to all patients according to the Declaration of Helsinki. All patients signed consent forms to participate in the study. This study was registered in the Iran Clinical Trial Registration site (IRCT201008094545N1).

RESULTS

Both groups were similar demographically (Table1). Overall, there were 100 ERCP procedures performed in 94 patients completed by a sphincterotomy for therapeutic reasons [group N = 23 cases (46%); group P = 22 cases (44%)]. In each group, there were 20 (40%) male patients and 30 (60%) female patients. The average procedure time and volume of consumed contrast agent was similar between groups (p=0.73). As seen in Figure 2, the diagnosis of ERCP was common bile duct (CBD) stone in 40% of cases (25 cases in group N; 15 cases in group P), PSC (3 cases), malignancy (18 cases), hydatid cyst (4 cases), SOD (9 cases), bile leakage (11 cases), and normal results (15 cases).

Table 1: Demographic characteristics of both groups (p=0.73)

Group	N-acetyl Cysteine (N) (%)	Placebo (P) (%)
Male	20 (40)	20 (40)
Female	30 (60)	30 (60)
Age, years (average)	60.9 (28-84)	55.38 (21-85)
Average volume of contrast agent	34.32 ml	31.12 ml
Average time of ERCP	21.76 min	22.7 min

The average amylase level in the N group was 80.7 u/ml and for lipase, it was 83.2 u/ml. In group P these values were 106.8 u/ml (amylase) and 91.7 u/ml (lipase). The average elevation after ERCP in the N group was 154.4 u/ml (amylase) and 143.9 u/ml (lipase), whereas in group P, it was 214.5 u/ml (amylase) and 209 u/ml (lipase).

After ERCP, there were 9 (18%) cases of abdominal pain recorded in group N and 16 (36%) in group P. The incidence of pancreatitis in group N was

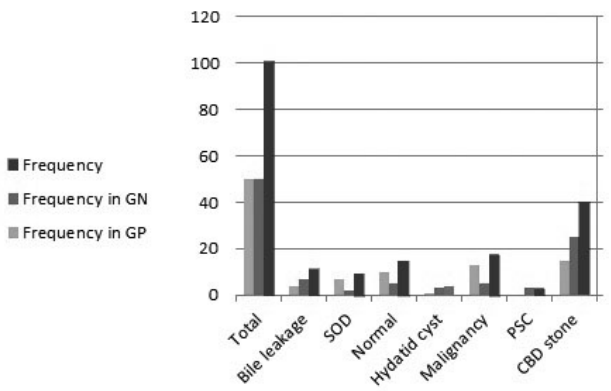

Fig. 2: Diagnosis of cases according to ERCP.(GN: group NAC, GP: group Placebo, SOD: sphincter of Oddi dysfunction, PSC: primary sclerosing cholangitis, CBD: common bile duct, each number represent number of cases)

5(10%) cases compared with 14 (28%) in group P, which showed a meaningful relation with an absolute risk reduction ratio of 18% (p=0.02; Table 2). The average length of admission in both groups was not significantly related (1.16±0.54 days in group N compared to 1.18±0.43 days in group P; p=0.8).

Table 2: Incidence of pancreatitis in both groups.

Group	No pancreatitis (%)	Pancreatitis (%)	Total
N-acetyl Cysteine (N)	45 (90)	5 (10)	50
Placebo (P)	36 (72)	14 (28)	50

DISCUSSION

Post-ERCP pancreatitis is the most important major complication of ERCP following prophylactic use of NAC as an anti-oxidant medication. The results of this study have shown a reduction in the rate of post-ECRP pancreatitis in the treated group [5 (10%)] compared with the placebo group [14 (28%)]. We can conclude that oral NAC may be useful for the prevention of post-ERCP pancreatitis, although the results of the current study differ from those of two previous studies that have used the intravenous injectable form of this drug.[9,17] This difference can be explained by the difference in efficacy of this drug as an oral solution or intravenous formula.

In a 2005 study in the USA, intravenous NAC was used for the prevention of pancreatitis both before and after ERCP. The results showed no difference between the therapeutic and placebo groups.[9] In the same year, another study was performed in the Netherlands that prescribed both the oral and intravenous forms of NAC with no significant prevention of pancreatitis.[17] In 2006, a study in Sweden reported that the local effects of the oral form of NAC reduced the concentration of NF-κB and lessened the severity of pancreatitis.[10] They proposed that the lack of efficacy of this drug in the two previous studies might have resulted from using the intravenous form. In the current study we used the oral form of this drug, which might explain the different results compared to the other studies.

In this study the number of need to treat (NNT) for NAC was 5, which according to the safety and relative low price of this drug, makes it a reasonable tool for the prophylaxis of this potentially dangerous side effect. The average duration of admission of patients in both groups was not significantly different (p=0.8). Thus most episodes of post-ERCP pancreatitis are mild, with less than 4 days of hospital stay, and consistent with the results of other studies.[4,5]

According to the results, the theories and practical aims of this study have been proven. However, because there are no similar studies with this unique methodology, this trial has been performed as a pilot study with a small sample size. If these results are repeated in future studies, this would be a useful method for preventing post-ERCP pancreatitis. We propose that by using our data, a statistically meaningful population be calculated and a clinical trial designed and performed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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