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ORIGINAL ARTICLE – OPEN ACCESS

Efficacy of N-acetyl Cysteine in Patients with Dyspepsia with Negative *Helicobacter pylori* Infection

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ABSTRACT

Objective: In this study, we evaluated the efficacy of NAC in dyspepsia symptoms in *Helicobacter pylori (H. pylori)* negative dyspeptic patients.

Materials and Methods: In this randomized clinical trial, 85 patients with functional dyspepsia without H. pylori infection underwent treatment with a proton pump inhibitor (PPI) pantoprazole 40mg daily (n=41) with or without NAC 600mg twice a day (n=44) for 8 weeks. Patients' clinical symptoms and change in the severity of dyspepsia symptoms were compared between the groups.

Results: Common symptoms were epigastric pain and bloating. The intervention group had significantly more cases with retrosternal burn and bloating and less early satiety as compared to the control group. In both intervention and control groups dyspepsia severity was significantly reduced from 5.26±2.06 and 4.68±2.81 to 1.87±1.38 and 2.22±2.04, respectively ($p<0.001$). The percent of reduction in dyspepsia severity in intervention group was significantly higher than control group (-66.25±23.44% vs. -50.14±35.02%, $p=0.01$).

Conclusion: PPI is an effective treatment for functional dyspepsia and NAC as an adjuvant to a PPI is a safe medication that can increase the response rate and treatment efficacy.

Keywords: Functional dyspepsia, N-acetyl cysteine; Proton pump inhibitor

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INTRODUCTION

Dyspepsia is a reoccurring chronic disorder that decreases quality of life. It is associated with several gastrointestinal (GI) symptoms including bloating, abdominal pain, early satiety, heartburn and nausea in the absence of underlying organic or metabolic diseases (1). Dyspepsia occurs in about 10% of the population and is more common in women than men (2).

Increased visceral sensitivity and decreased gastric emptying are reported in dyspepsia. Various mechanisms, such as duodenal sensitivity to lumen content, intestinal dysmotility, psychologic disorders, nervous system disorders, and *H. pylori* infection are proposed to be involved in dyspepsia (3).

There are several proposed mechanisms for the cause of dyspepsia. Acute inflammation secondary to an infection contributes to the development of dyspepsia (2). Oxidative stress and inflammation have been reported in the development of dyspepsia in animal studies (4). As such, treatment with rifaximin improves symptoms of dyspepsia by inducing its anti-inflammatory effects (5).

N-acetyl cysteine (NAC) is an amino acid derivative containing thiol and a precursor of glutathione intracellular antioxidants. NAC has potential antioxidant effects; it eliminates reactive neutrophils and facilitates the eradication of free radicals through conjugation or reduction reactions (6). It also suppresses cytokine expression and inhibits the Kappa B nuclear factor (7).

Recently, increasing attention has been paid to NAC's therapeutic abilities in various diseases, in which the main cause is considered to be oxidative stress, cellular degeneration, and inflammation (8). Several studies have shown that lipid peroxidation and protein oxidation are a major consequence of the production of free oxygen radicals (9), which play an important role in the development of stomach ulcers. In this regard, thiol-containing compounds such as NAC, could reduce mucosal gastric damage caused by various factors causing ulceration (10).

H. pylori plays an important role in the development of gastritis, gastroduodenal ulcer, and gastric cancer (11). Most patients referred for treatment of HP usually have dyspepsia (12). In some studies, NAC has been used as an adjunct to HP eradication treatment, with high efficacy possibly due to its antioxidant and anti-inflammatory properties (13, 14).

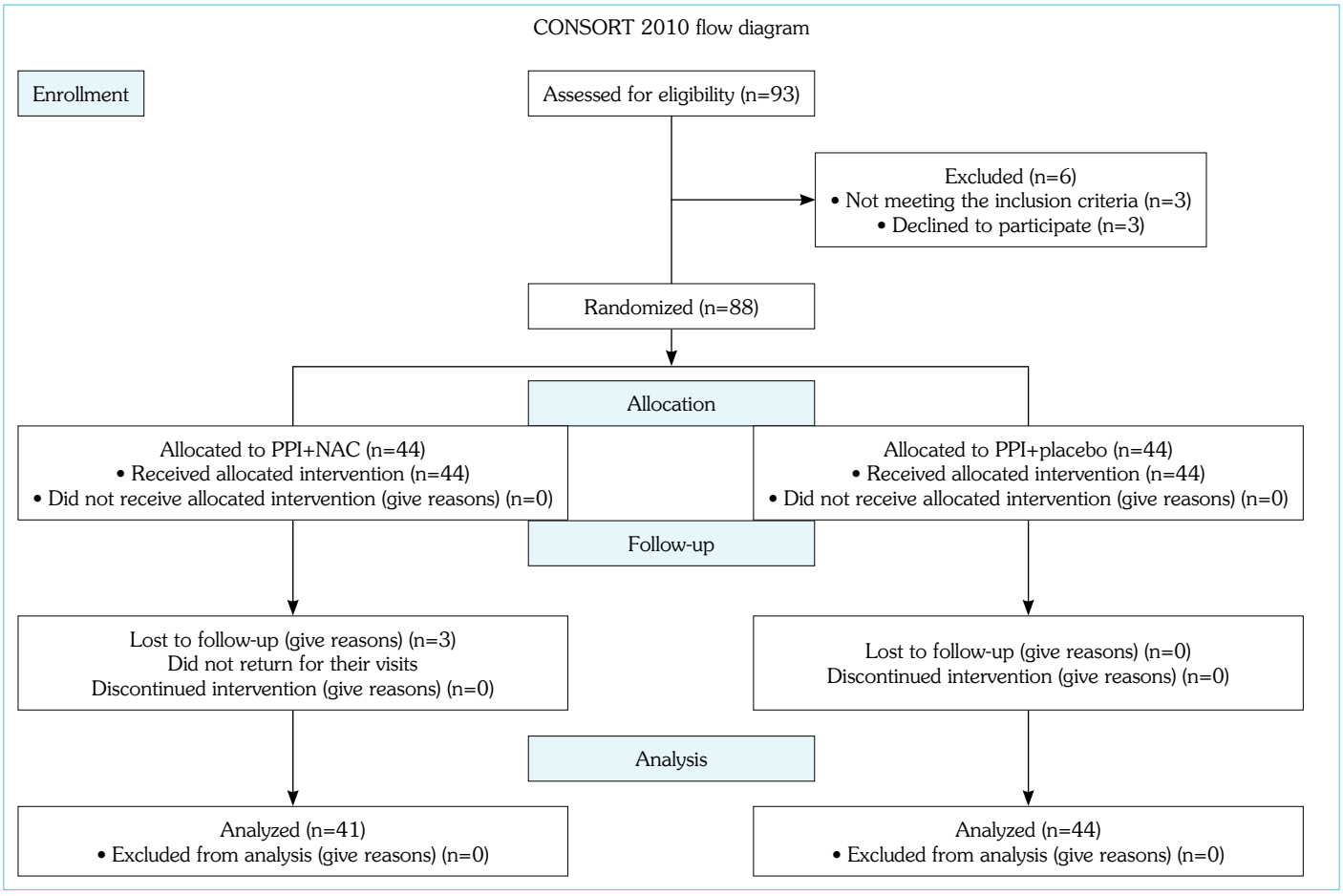

Figure 1. CONSORT flow diagram

The anti-inflammatory and gastro-protective effects of NAC can also be extended in dyspeptic patients without HP infection. In this study, we aimed to evaluate the efficacy of NAC in improving the symptoms of dyspepsia in dyspeptic and HP negative patients.

MATERIALS and METHODS

In this randomized controlled clinical trial, 88 patients with dyspepsia with negative HP infection visiting Gastroenterology clinics at Imam Khomeini Hospital during January 2018 to October 2018 were recruited. These patients presented with dyspepsia with no indication for diagnostic endoscopy and had either negative stool antigen or urea breath test for HP. Exclusion criteria were chronic use of Non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for more than one month; gastric outlet obstruction diagnosed by endoscopy; pregnancy; chronic kidney disease; gastrointestinal malignancy; previous gastric surgery; and patients with asthma or chronic obstructive pulmonary disease receiving NAC. Use of PPIs were not a contraindication for inclusion in the study. All patients gave written informed consent.

The study sample size for each group was calculated to be 34 cases considering an effect size of d ≥0.7 as statistically significant in a two-tailed test with α=0.05 and power of 0.80. Since it was possible that some patients would not complete the study, we included 44 patients in each group. Using random number blocks and sealed envelopes, patients were randomly allocated to pantoprazole 40 mg daily with NAC 600 mg twice daily orally (n=44) or pantoprazole 40 mg daily and placebo (n=44) twice daily orally for eight weeks (Fig. 1). Three patients left the study in NAC group during study period and did not complete the trial. The participants, outcome accessor and data analyzer were all blinded to the allocation groups.

Patient baseline characteristics including age, gender, underlying diseases and dyspepsia signs and symptoms were recorded. Dyspepsia was diagnosed according to ROME III criteria (13).

ROME III criteria is used when considering functional dyspepsia if the patient has epigastric pain along with one or more of the following symptoms for the previous three months with symptom onset and at least 6 months prior to diagnosis:

Bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning; and no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

Three questions were used to assess the dyspepsia symptoms: 1- pain or discomfort or burning in the upper abdomen or lower chest sometimes relieved by food or antacids, 2- early satiation 3- bothersome postprandial fullness. The answer to each was scored between 0–6 according to the severity of symptoms (zero for absence of symptom during the past three months and 6 for the most severe symptom). A drawing of the upper body abdomen and lower chest was added in the questionnaire to help patients localizing the

Table 1. Baseline findings and clinical symptoms of patients in both groups

	NAC group		Placebo group		p
	n	%	n	%	
Age (years) Mean±SD	41.07±10.87		38.63±7.28		0.22
Gender					
Male	18	43.9	24	54.5	0.32
Female	23	56.1	20	45.5	
Cardiac diseases	3	7.3	3	6.8	0.92
Diabetes mellitus	3	7.3	5	11.4	0.71
Previous gastrointestinal bleeding	1	2.4	0	0	0.48
Presenting symptoms					
Epigastric pain	32	78	30	68.2	0.30
Vomiting	11	26.8	8	18.2	0.33
Early satiation	17	41.5	30	68.2	0.01
Retrosternal burn	32	78	12	27.3	<0.001
Belching	25	61	10	22.7	<0.001
Bloating	33	80.5	28	63.6	0.08

NAC: N-acetyl cysteine; SD: Standard deviation

area of discomfort. Total score of dyspepsia symptoms (0–18) was used to indicate the severity of dyspepsia (15).

Statistical Analysis

All data were analyzed using SPSS20 (version 22; SPSS Inc., Chicago, IL). The analysis are conducted per protocol. The results are expressed as mean±standard deviation or percentage. Kolmogorov-Smirnov test was used to assess normal distribution of data. Levene test was applied to test the variance homogeneity. Pearson chi-square analysis and Fisher exact test, independent T-test or Mann-Whitney U test were used to compare data between groups and Wilcoxon rank test was used to compare dyspepsia severity before and after intervention in each group. p-values of less than 0.05 were considered statistically significant.

RESULTS

Two groups were similar regarding baseline characteristics (Table 1). Epigastric pain and bloating were the most common presenting symptoms in both groups. The NAC group had significantly more retrosternal burn and belching with lower rate of early satiety (Table 1).

Table 2 demonstrates the dyspepsia severity before and after intervention in each group and percent change in the severity. While NAC group had significantly higher rate of reduction in the dyspepsia severity, there was no significant difference in severity before or after intervention in between the groups. In both groups, dyspepsia severity was reduced after intervention compared to baseline severity ($p<0.001$, for both).

Table 2. Dyspepsia severity before and after intervention and percent change between groups

Dyspepsia severity	NAC group	Placebo group	p
Before intervention	5.26±2.06	4.68±2.81	0.27
After intervention	1.87±1.38	2.22±2.04	0.36
Percent change	-66.25±23.44	-50.14±35.02	0.01

SD: Standard deviation

DISCUSSION

Majority of dyspeptic patients respond to medical treatments and dietary regimens. PPIs are the most commonly used drugs, but the underlying mechanism for their effectiveness is unclear. A meta-analysis has shown that PPIs have been helpful in improving functional dyspepsia symptoms, suggesting that a portion of patients may have an acid-dependent disorder (16). In a recent review, PPIs were more effective than placebo but had no association with functional dyspepsia subtypes (17).

In this study, both groups were treated with PPIs as primary treatment and NAC was added as an adjuvant to the main therapy. In both groups, the severity of the symptoms of dyspepsia was significantly reduced, indicative of the efficacy of PPI in these patients. On the other hand, these results indicate that the treatment is more effective by adding NAC due to the more reduction in dyspepsia severity in NAC group.

NAC has been used to treat and improve the quality of life in patients with cystic fibrosis and other pulmonary diseases, for the treatment of drug toxicity (e.g. acetaminophen toxicity), contrast-induced nephropathy, cardiovascular disease and diabetes. NAC also has anti-cancer and anti-inflammatory properties and has also been shown to be effective in the treatment of HIV (8). NAC produces antioxidant and anti-toxin effects by increasing the level of glutathione and protection against free radicals (18, 19).

Studies have demonstrated that administration of NAC to the gastric tissue reduces the activity of cytokines. In fact, NAC has gastroprotective and anti-inflammatory effects and these gastroprotective effects are due to the NAC's antioxidant properties (20). It has also been stated that the gastroprotective effects of NAC are also due to its anti-secretory effects (21). In another study, Soliman et al. (22) concluded that NAC's gastroprotective role is due the anti-oxidative, anti-apoptotic and anti-inflammatory mechanisms.

The effectiveness of NAC in the treatment of HP eradication has also been evaluated. Karbasi and colleagues (23) found that the addition of NAC to sequential therapy for HP accompanies with a higher rate of HP eradication in patients with dyspepsia and positive HP testing; this could be caused by reducing the mucosal layer thickness and increasing the permeability to antibiotics. Yoon et al. (14) also observed that the group treated with NAC and routine eradication therapy had significantly higher eradication rate.

It is proposed that an infection, a change in microbial flora or a food allergen, cause an increase in duodenum permeability and eosinophilia with or without increasing mast cells; which subsequently activates a mucosal immune response. Local gastroduodenal responses to low-grade inflammation, alters the gastroduodenal function and leads into dysfunction in the relaxation of the fundus in some patients. In addition, circulating cytokines such as TNF-α can cause systemic and neurological symptoms such as anxiety (24).

Regarding various effects of NAC including antioxidant, anti-microbial, oxidative stress protection and proven gastroprotective effects in recent studies, it may be concluded that NAC, through a combination of these mechanisms, accelerates the recovery of the symptoms in patients with functional dyspepsia.

In addition to these effects of NAC, there was no reported drug side effect in any of the patients, making NAC a possibly safe and effective medication in treatment of patients with functional dyspepsia in combination with a PPI.

In conclusion, PPI is effective in the treatment of functional dyspepsia and NAC, as an adjuvant therapy, is a safe and effective treatment in patients with functional dyspepsia.

Ethics Committee Approval: The ethical committee of Ardabil University of Medical Sciences have approved the study protocol (Decision Date: 01.14.2018 /Decision No: IR.ARUMS.REC.1396.208).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: NH, KI, MN, AH. Performed the experiments or case: NH, MN. Analyzed the data: MH, CL. Wrote the paper: MH, CL, AH, KI. All authors have read and approved the final manuscript.

Conflict of Interest: The authors declare there is no conflict of interest.

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