

N-acetyl cysteine as an adjunct to standard anti-*Helicobacter pylori* eradication regimen in patients with dyspepsia: A prospective randomized, open-label trial

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Abstract

Background: Increasing antibiotic resistance of *Helicobacter pylori* (*H. pylori*) which is associated with diseases of the upper gastrointestinal tract, has made alternative treatments necessary. This study compares the efficacy of adding N-acetyl cysteine (NAC) to standard regimen for *H. pylori* eradication.

Materials and Methods: We conducted a randomized, open-label trial, comparing the efficacy of 14 days of quadruple therapy with Amoxicillin, Bismuth citrate, Omeprazole, Clarithromycin (group A) versus 14 days of above regimen plus NAC (group B) in adult patients with dyspepsia. Primary objective was *H. pylori* eradication. Compliance and side effects were determined by questionnaires. Our analysis was by intention-to-treat (ITT) and per-protocol. This study is registered with www.IRCT.ir, number: IRCT201201078634N1.

Result: A total of 121 participants aged 21-76 years with a mean age of 44.5 ± 14.1 , and 52.9% female, were randomly allocated a treatment: 60 with 14-day standard therapy and 61 with 14-day standard therapy with NAC. The eradication rate in groups A and B with ITT analyses was 49/60 (81.7%; 95% [confidence intervals] CI = 71.6-91.8%) and 50/61 (82%; 95% CI = 72-91.9%), respectively ($P = 0.96$). In per-protocol analysis, the rate of *H. pylori* eradication in groups A and B was 45/54 (83.3%; 95% CI = 73.1-93.6%) and 45/53 (84.9%; 95% CI = 74.9-94.9%), respectively ($P = 0.82$). Minor well tolerated side effects were reported in 15 (34.9%) and 21 (35.6%) patients of groups A and B, respectively, and only one therapy cessation in group A was created.

Conclusion: Standard 14-day triple-drug therapy with NAC is not preferable to standard drug regimens for *H. pylori* infection.

Key Words: *Helicobacter pylori*, *Helicobacter pylori* eradication, N-acetyl cysteine

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is the most prevalent gastric microbial pathogen; it affects almost half of the world's population and plays a major role in the pathogenesis of non-ulcer dyspepsia, peptic ulcer disease, and gastric tumors, including both low-grade mucosa-associated lymphoid tissue lymphoma and adenocarcinoma.^[1-4]

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H. pylori is mainly acquired before the age of 5 years. Generally, in the absence of treatment, it remains for life and was classified as grade 1 carcinogen by the World Health Organization in 1994.^[3,5,6] Infected patients had 10-15% lifetime risk for a definite morbidity and mortality, including 10-20% lifetime risk to develop peptic ulcer disease and two to six-fold higher relative risk to develop gastric cancer.^[5,7,8]

Despite the evidence that *H. pylori* prevalence is declining in developed countries, the infection remains widespread internationally with near 90% prevalence in adults older than 35 years in Iran.^[4,9,10]

A triple therapy using proton pump inhibitor (PPI) and 2 antibiotics or a quadruple therapy, which includes bismuth to the triple therapy, are recognized as the most effective and most recommended eradication therapies and are widely used.^[8,11]

Eradication criteria were defined in the Maastricht III Report, published by the European *H. pylori* Study Group in 2005. Test-and-treat is an accepted approach in high-prevalence locations and recommendation for first choice of treatment include triple therapy using a PPI with clarithromycin and amoxicillin or metronidazole administered twice daily for 7-14 days.^[8]

Eradicated rate must be higher than 80% on an intention-to-treat (ITT) basis with first-line therapeutic regimens.^[12]

Therefore, curing such an infection and optimal treatment still remain a challenge and multiple trials with differences in number, type, dosing of drugs, and length of treatment performed.^[13] No current therapy achieves bacterial eradication in all treated patients and eradication rates for *H. pylori* might be suboptimal (<80%) worldwide.^[13,14]

For instance, studies performed in the United States and Europe as a developed country have shown that the eradication rate has dropped below 85%.^[8,15]

During the last decade, the efficacy of standard 7-14-day triple therapies decreased to approximately 70% in many areas, mainly due to increasing primary bacterial resistance to antibiotics.^[16,17]

Data from two large trials found that after 14-day triple therapy, the eradication rate was 70% in non-ulcer dyspepsia patients, and 81.7% in peptic ulcer patients.^[18,19] The rates of resistance to clarithromycin and metronidazole have been increasing gradually; however, resistance to amoxicillin is not increasing,

thereby making this antibiotic an essential choice for *H. pylori* eradication regimen.^[20,21] In a recent study in Iran, the approximate rates of drug-resistant *H. pylori* isolates were 64.6% to metronidazole and 17.1% to clarithromycin.^[22] To increase first-line triple therapy eradication rates, several clinical trials have been initiated involving the use of quadruple therapy as a first-line therapy, or the addition of adjunct, respectively, such as N-acetyl cysteine (NAC) to triple therapy.^[8,23] NAC as a mucolytic and a thiol-containing antioxidant is a novel agent and has been investigated in the treatment of *H. pylori*, which inhibits the growth of the bacteria but did not eradicate it.^[24] NAC disrupts the disulfide bonds of glycoproteins in mucus gel layer, enhances intracellular synthesis of glutathione, provides a direct access for potential therapy in gastric mucosa, and reduces damage caused by *H. pylori* infection.^[25,26] This study evaluates the impact of adding NAC to quadruple regimens of *H. pylori* eradication.

MATERIALS AND METHODS

This randomized, open-label, phase 3 trial was performed in Isfahan University of Medical Sciences. All patients between 17 and 80 years of age complaining of dyspeptic symptoms who referred to the Gastroenterology Clinics of Al-Zahra hospital, Noor, Poursina Hakim Research Center and Ardakan hospital for endoscopy by a gastroenterologist between September 2010 and July 2012 recruited with full consent if *H. pylori* tests were positive (confirmed by histology, rapid urease test, or stool antigen test). We prospectively assessed 180 consecutive subjects with *H. pylori*-positive complaining of dyspeptic symptoms. This study was approved by the local ethics committee. The enrolled patients were informed about the possible side effects associated with drug therapy and the possibility of eradication failure. Patients having previously received eradication of *H. pylori* treatment, presence of underlying disease such as cirrhosis, renal failure, severe cardiac disease, malignancy outside the gastrointestinal (GI) tract, the need for simultaneous use of non steroid anti inflammatory drugs (NSAIDs), the need for concomitant use of steroids or other immunosuppressive drugs, recent gastrointestinal bleeding, pregnancy, or lactating mothers were excluded from the study. Patients were randomly assigned in one of two *H. pylori* eradication regimens: Amoxicillin (from farabi co. Iran) 500 mg 4 times daily, Bismuth citrate (from arya co. Iran) 120 mg 4 times daily, Omeprazole (from abidi co. Iran) 20 mg twice daily, and Clarithromycin (from tolidarou co. Iran) 500 mg twice daily as standard therapy with and without effervescent flumucil (NAC from swiss zambon co. swiss) 600 mg tablets twice daily for 14 days. Four to six weeks after termination of

H. pylori eradication regimens, *H. pylori* stool antigen test (generic assay-Dahlewitz-Germany) was performed to evaluate the effectiveness of the eradication. If the *H. pylori* stool antigen test result was negative, successful eradication was considered. Compliance and side effects with therapy were determined by a specific questionnaire completed by the participants during the treatment period. If more than 85% of the prescribed drugs are consumed, good compliance was considered. The eradication rates, their 95% confidence intervals (CI) at ITT analysis (all included patients), and per protocol (PP) analysis (all patients who took >85% of prescribed treatment) were calculated. Statistical analysis was performed with the Chi-square test, Fisher's exact test, and the Independent *t*-test. *P* values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). This study is registered with www.IRCT.ir, number: IRCT201201078634N1.

RESULT

Although 180 patients enrolled, only 121 cases of them completed follow-up and 1 case dropped out because of drug intolerance. A total of 107 (87.2%) patients took >85% of the prescribed treatment, which was considered good compliance. Participants were in the age group 21-76 years with a mean age of 44.5 ± 14.1 and included 52.9% females; they were randomly allocated two anti-*H. pylori* eradication regimens. There were 60 patients in the amoxicillin, bismuth, clarithromycin, omeprazole (ABCO) group and 61 patients in the amoxicillin, bismuth, clarithromycin, omeprazole, NAC (ABCON) group [Table 1]. There was no statistical difference between the two groups regarding age, gender distribution, smoking history, side effects, drug tolerance, and indication of treatment. There was no statistically significant difference between the two groups in terms of eradication rate as per ITT and PP analysis.

There was only one drop out in the ABCO group with significant side effects, leading to therapy cessation before completion of treatment. The incidence and tolerability of side effects were not statistically different between the ABCO and ABCON groups [Table 1]. The most frequent side effects were nausea, vomiting, and abdominal discomfort [Table 2]. Vomiting was significantly more common in the ABCON groups. All side effects were mild and tolerated.

DISCUSSION

This study demonstrated that the eradication rate of standard 14-day triple-drug therapy containing

bismuth subcitrate was not improved with the addition of NAC.

This is in contrast with the study by Aslam *et al.*, which shows positive effects of NAC; this was believed to be due to mucus-dissolving properties and the capability to reduce and prevent biofilm formation.^[27] In addition, Zala *et al.* reported that NAC at 1.2 g twice a day for 10 days improved the eradication chances of *H. pylori* in smokers who were concomitantly treated with omeprazole and amoxicillin.^[28]

In another study, NAC showed an additive effect on the eradication rates of *H. pylori* obtained with dual therapy with lansoprazole and clarithromycin.^[29]

In addition, the study by Huynh *et al.* showed that NAC inhibits *H. pylori* growth both *in vitro* and *in vivo* and reduced bacterial load in infected mice.^[24]

High prevalence of *H. pylori* infection in developing countries warrants further studies to identify the best treatment options.

Table 1: Demography and *Helicobacter pylori* eradicated rate (intention-to-treat and per protocol)

Group	ABCO*	ABCON**	<i>P</i> value
Patient number	60	61	
Age (y/o)**	42.3±13.9	47.1±13.9	0.08
Gender (F/M)	33/27	31/30	0.65
Indication of treatment (%)			
NUD 44	44 (44.2)	48 (65.9)	0.27
DU 15	15 (38.5)	10 (22.7)	0.24
GU 1	1 (1.9)	3 (9.1)	0.6
Side effect (%)	15 (34.9)	21 (35.6)	0.94
Smoking history (%)	2 (4.5)	7 (14)	0.17
<i>H. pylori</i> eradicated success rate			
Intention-to-treat (%)	49/60 (81.7)	50/61 (82)	0.96
95% CI*** (%)	71.6-91.8	72-91.9	
Per-protocol (%)	45/54 (83.3)	45/53 (84.9)	0.82
95% CI*** (%)	73.1-93.6	74.9-94.9	

*Amoxicillin, bismout, clarithromycin, omeprazole, **Amoxicillin, bismout, clarithromycin, omeprazole, N-acetyl cysteine, **Data presented as mean±standard deviation, ***95% Confidence interval, *H. pylori: Helicobacter pylori*, NUD: Non ulcer dyspepsia, DU: Duodenal ulcer, GU: Gastric ulcer, CI: Confidence interval, ABCO: Amoxicillin, bismuth, clarithromycin, omeprazole, ABCON: Amoxicillin, bismuth, clarithromycin, omeprazole, N-acetyl cysteine

Table 2: Side effects, type and incidence

Group	ABCO (%)	ABCON (%)	<i>P</i> value
Nausea	8 (13.3)	12 (19.7)	0.35
Vomiting	4 (6.7)	12 (19.7)	0.03
Headache	5 (8.3)	8 (13.3)	0.4
Abdominal discomfort	10 (16.7)	9 (14.8)	0.77
Diarrhea	7 (11.7)	9 (14.8)	0.6
Skin rash	0 (0)	1 (1.6)	1

ABCO: Amoxicillin, bismout, clarithromycin, omeprazole; ABCON: Amoxicillin, bismout, clarithromycin, omeprazole, N-acetyl cysteine

Many trials including various antibiotic combinations, longer duration therapy, quadruple therapy, sequential therapy, adjuvant therapy, or new antimicrobial-based therapies have been performed in an attempt to improve the eradication rate; however, 100% rate is yet to be achieved.

Decreases in eradication rates may be attributed to antibiotic resistance, which develops due to frequent and uncontrolled use. Avoiding antibiotics that the patient has previously used for *H. pylori* eradication or other illnesses will increase and increasing the duration of treatment has been shown to improve the eradication rate.^[30,31]

H. pylori creates a defensive microenvironment in the gastric mucosa for the purpose of protecting itself and causes inflammation. Oxidative stress and accumulation of reactive oxygen metabolites play a major role in *H. pylori*-induced mucosal damage.^[26]

Several recent reports indicate that *H. pylori* forms biofilm, a self-produced matrix, either *in vitro* or *in vivo* with organisms embedded on it. Hence, persistent *H. pylori* infection may be related to biofilm formation in the gastric mucosal epithelial cells.^[32-35]

It is conceivable that the combination of anti-biofilm and antimicrobial agents would provide synergy and novel biofilm-targeting therapies could be beneficial by killing biofilm-encased bacteria.^[35,36]

Therefore, there is a need for novel drugs and adjuvants to eliminate bacterial defense mechanisms as an important issue in the eradication of *H. pylori*.^[37] NAC treatment prior to starting antibiotic therapy allowed the disappearance of gastric biofilms in all patients in whom *H. pylori* was eradicated.^[35] NAC has a mucolytic, antioxidant, and antibacterial activity. It also provides a cysteine source for the intracellular synthesis of glutathione.^[38] NAC changes the physicochemical properties of the gastric mucus gel, impairs the microenvironment created by *H. pylori*, and provides an appropriate environment for antibiotics to affect.^[25] The antibacterial effect of NAC was previously shown against both Gram-positive and Gram-negative microorganisms and was believed to be predominantly bacteriostatic.^[39] NAC is a safe, inexpensive, and well-tolerated antioxidant and in dosages of 1,200 mg twice daily or lower, it is well tolerated. Side effects are unusual but may include nausea, vomiting, diarrhea, transient skin rash, flushing, epigastric pain, and constipation.^[40,41] Drug compliance was good and overall side effects were not statistically different between the ABCO and ABCON groups; however, vomiting was found to be

more common in the ABCON group, which can be due to the added effect of NAC. Further studies need to be conducted with larger cohorts of subjects to study the adjuvant effects of NAC, both along and prior to the *H. pylori* eradication regimes, to determine the potential role of NAC-based therapy.

The only limitation of this study was the loss of follow-up of many patients for performing post-eradication stool antigen test.

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