The Effect of N-Acetyl Cysteine on Laryngopharyngeal Reflux

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Abstract- Laryngopharyngeal reflux (LPR) is a variant of gastroesophageal reflux disease (GERD) in which the stomach contents go up into the pharynx and then down into the larynx. LPR causes a wide spectrum of manifestations mainly related to the upper and the lower respiratory system such as laryngitis, asthma, chronic obstructive pulmonary disease, cough, hoarseness, postnasal drip disease, sinusitis, otitis media, recurrent pneumonia, laryngeal cancer and etc. The object of this study was to examine the effect of N-acetyl Cysteine (NAC) with and without Omeprazole on laryngitis and LPR. Ninety patients with laryngitis or its symptoms were referred and randomly assigned into three groups. The first group was treated by Omeprazole and NAC. The second group was treated by Omeprazole and placebo and the last group was treated by NAC and placebo. Duration of treatment was 3 months and all patients were evaluated at the beginning of study, one month and three month after treatment of sign and symptoms, based on reflux symptom index (RSI) and reflex finding score (RFS). Based on the results of this study, despite therapeutic efficacy of all treatment protocols, the RSI before and after 3 months treatment had significant difference in (NAS+ Omeprazole) and (Omeprazole+ placebo) group (P<0.001 in the first group, P<0.001 in the second group and P=0.35 in the third group). Whereas RFS before and after 3 month treatment had significant difference in all groups. (P<0.001 in each group in comparison with itself) but this results had not significant difference after 1 month treatment. Our results showed that the combination therapy with Omeprazole and NAC treatment had the most effect on both subjective and objective questionnaire at least after 3 months treatment. Based on the results of the present study, it seems that the use objective tools are more accurate than subjective tools in evaluation of therapeutic effects in patients with GERD-related laryngitis.

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Keywords: Laryngopharyngeal reflux; N-acetyl Cysteine; Omeprazole

Introduction

Gastroesophageal reflux disease (GERD) is a common medical condition affecting approximately 35-40% of the adult population in the western world (1). In contrast to GERD, the prevalence of Laryngopharyngeal reflux (LPR) in the general population is not known. LPR is a variant of GERD that causes a wide spectrum of manifestations mainly related with the upper and the lower respiratory system such as laryngitis, asthma, chronic obstructive pulmonary disease, cough, hoarseness, postnasal drip disease, sinusitis, otitis media, recurrent pneumonia and laryngeal cancer (2). However, classical symptoms of GERD are absent in more than half of the patients with suspected LPR (3). And endoscopic evidence of erosive esophagitis is absent in these patients (4). But some of these patients complain of chronic hoarseness, cough, throat-clearing, sore throat, dysphagia and etc. In this condition, the history of presentation, physical examination and laryngoscopy may rule out cancer, and at last these patients are diagnosed as LPR. In previous studies, it has been shown positive results associated with anti-reflux treatments such as H_2 blocker and proton pump inhibitors (PPI) in management of reflux and extra-esophageal complications (5). Several studies believe that because PPI therapy is easy and appears to be safe, patients with extra-esophageal symptoms, thought to be related to reflux, and should undergo a trial of twice-daily PPI therapy for at last 2 months (6-11). If the

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patient responded to the treatment, tapering to once-daily and then it would be prudent to minimal acid suppression to control of symptoms (12,13). In unresponsive patients, testing with impedance and/or pH monitoring may be is the best alternative to rule out reflux as the cause and then move forward to consider other causes for patients with continued symptoms (14). In contrast to Omeprazole, there are no more study about the effect of N-acetyl cysteine (NAC) as mucolytic agent on laryngitis and LPR. In this study we assessed the effect of NAC with and without Omeprazole on laryngitis.

Materials and Methods

In this clinical trial study, ninety patients with laryngitis or its symptoms referred to ENT clinic of Amir Alam Hospital in Tehran were enrolled in a randomized controlled, double–blinded study. At first this patients filled a questionnaire about their symptoms (subjective sign) and had done laryngeal endoscopy (objective sign). Then all patients randomly assigned into three groups, the first group was treated by Omeprazole and NAC, the second group was treated by Omeprazole and placebo and the last group was treated by NAC and placebo.

In this study Omeprazole 20 mg (Darou Pakhsh Pharmaceutical Mfg. Co., Tehran, Iran) used twice daily (1 capsule/12 hours), NAC 600 mg (Sobhan Pharmaceutical Co., Tehran, Iran) used once daily and placebo that were presented in a matching capsule with Omeprazole and NAC used once daily in the second group and twice daily (1 capsule/12 hours) in the third group.

Randomization was performed by means of sealed opaque envelopes containing computer generated random number. None of patients and physicians had any awareness about drug protocol content and just drug store manager was aware of the drug protocol contents.

Patients presenting with subjective sign, based on reflux symptom index (RSI): 1. Hoarseness or a problem with voice, 2. Throat clearing, 3. Excess throat mucus or postnasal drip, 4. Difficulty swallowing food, liquids or pills, 5. Coughing after ate or lie down, 6. Breathing difficulties or choking episodes, 7. Troublesome or annoying cough, 8. Sensations of something sticking in your throat or a lump in your throat 9. Heartburn, chest pain, indigestion, or stomach acid coming up and objective endoscopic sign based on reflex finding score (RFS): 1. Pseudosulcus, 2. Ventricular obliteration, 3. Erythema and hyperemia of larynx, 4. Vocal cord edema, 5. Diffuse laryngeal edema, 6. Post commissural hypertrophy, 7. Subglottic granuloma and granulation tissue and 8. Thick endolaryngeal mucus were eligible for inclusion. Exclusion criteria included age of younger than 12 years, RFS less than 7 (because RFS over than 7 has significant correlation with pH metry), patients who has positive history of drug reaction to NAC, positive history of previous reflux treatment, laryngeal cancer and, laryngitis sicca or inability to consent for the study.

Duration of treatment was 3 months. All patients were evaluated at the beginning of study, one month and three months after treatment of objective and subjective sign on the basis of RSI and RFS, which are validated clinical tools for LPR (15,16).

The collected data were analyzed by the SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA) and independent Chi-square and t-test. Continuous data were demonstrated as mean±standard deviation. *P*-value less than 0.05 were considered significant. The study was approved by the ethics committee of the university before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration. All patients were informed about the study protocol and the written consent was obtained from the participants.

Results

A total of ninety patients in this study 45 (50%) were men and 45 (50%) were women. Mean age was 40±12.57 years. All patients were classified in three groups and were well balanced with respect to age and sex.

At the beginning of study hoarseness or a problem with voice was common subjective finding in the first and the second groups with 3.4±1.4 and 3.1±1.4 score respectively, whereas excess throat mucus or postnasal drip with 3.3±1.3 score was common finding in the third group. Also erythema and hyperemia of larynx was common objective finding in all groups. As well as vocal cord edema was the only finding that was not balanced in all group at the beginning of the study and was higher in the first group. The other findings were not significantly different among the groups (Tables 1 and 2).

After 1st month of treatment, erythema and hyperemia of larynx were the only findings that were significantly different in all group ($P<0.01$). The other objective and subjective findings were not different after 1 month treatment (Tables 3 and 4). Also objective and subjective findings before and after 1 month treatment were not significantly different within each group.

Table 1. Comparison of RSI before treatment in all groups.

Parameter	NAC + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Hoarseness or a problem with voice	3.4±1.4	2.6±1.2	3.1±1.4	0.07
Throat clearing	2.9±1.6	2.7±1.3	3.2±1.6	0.39
Excess throat mucus or postnasal drip	2.9±1.6	3.3±1.3	3.0±1.6	0.54
Difficulty swallowing food, liquids or pills	0.9±1.3	0.7±0.9	0.7±1.3	0.63
Coughing after you ate or lie down	1.5±1.5	0.7±1.2	1.4±1.6	0.56
Breathing difficulties or choking episodes	1.4±1.5	0.6±1.1	0.9±1.3	0.07
Troublesome or annoying cough	0.8±1.6	0.7±1.1	0.5±1.1	0.17
Sensations of something sticking in your Throat or a lump in your throat	2.4±1.8	2.3±1.3	2.3±1.5	0.77
Heartburn, chest pain, indigestion, or Stomach acid coming up	2.6±1.3	2.4±1.7	2.6±1.4	0.90
Total	19.1±6.3	16.3±5.0	18.0±6.0	0.31

Table 2. Comparison of RFS before treatment in all groups.

Parameter	NAC + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Pseudosulcus	0.4±0.8	0.6±0.3	0.4±0.8	0.10
Ventricular obliteration	0.8±1.1	0.8±0.9	0.7±0.9	0.96
Erythema and hyperemia of larynx	2.6±0.9	2.0±1.7	2.3±1.1	0.13
Vocal cord edema	1.6±1.0	0.8±0.6	1.2±0.5	0.00*
Diffuse laryngeal edema	0.6±0.8	0.4±0.8	0.7±0.7	0.16
Post commissure hypertrophy	1.4±0.7	1.4±0.6	1.4±0.8	0.83
Subglottic granuloma and granulation	0.0±0.0	0.0±0.0	0.0±0.0	-
Thick endolaryngeal mucus	0.6±0.9	0.3±0.7	0.3±0.7	0.20
Total	7.8±3.3	5.9±2.8	7.2±2.9	0.10

Table 3. Comparison of RSI after 1 month treatment in all groups.

Parameter	NAC + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Hoarseness or a problem with voice	2.4±1.2	2.4±1.1	2.9±1.8	0.06
Throat clearing	2.0±1.1	2.5±1.6	3.0±1.6	0.48
Excess throat mucus or postnasal drip	2.1±1.2	3.1±1.3	3.0±1.5	0.66
Difficulty swallowing food, liquids or pills	0.8±0.3	0.7±0.1	0.7±1.1	0.80
Coughing after you ate or lie down	1.3±1.5	0.7±0.5	1.0±1.5	0.65
Breathing difficulties or choking episodes	1.1±1.1	0.6±0.6	0.8±1.2	0.06
Troublesome or annoying cough	0.7±0.6	0.5±0.8	0.7±1.8	0.13
Sensations of something sticking in your Throat or a lump in your throat	2.0±1.5	1.9±1.3	2.2±1.5	0.55
Heartburn, chest pain, indigestion, or Stomach acid coming up	1.9±0.3	1.9±1.7	2.5±1.7	0.76
Total	15.0±0.8	16.0±2.2	16.1±5.8	0.23

After 3 month our results showed several subject findings such as: 1. Difficulty swallowing food, liquids or pills, 2. Coughing after ate or lie down and 3. Breathing difficulties or choking episodes. Despite the

efficacy of treatments there was no significant difference before and after investigation in all groups (Table 5). This condition also repeated about several objective findings such as: 1. Pseudosulcus, 2. Vocal cord edema and 3. Thick endolaryngeal mucus was not significantly different in all 3 groups (Table 6).

Table 4. Comparison of RFS after 1 month treatment in all groups.

Parameter	NAC + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Pseudosulcus	0.4±0.8	0.1±0.5	0.2±0.6	0.26
Ventricular obliteration	0.5±0.8	0.2±0.6	0.7±0.3	0.11
Erythema and hyperemia of larynx	2.6±0.9	1.6±1.0	1.8±0.9	<0.001*
Vocal cord edema	1.0±0.8	0.9±0.4	1.1±0.8	0.66
Diffuse laryngeal edema	0.2±0.4	0.4±0.8	0.4±0.7	0.07
Post commissure hypertrophy	1.0±0.6	0.1±0.5	1.2±0.7	0.31
Subglottic granuloma and granulation	0.0±0.0	0.0±0.0	0.0±0.3	0.36
Thick endolaryngeal mucus	0.1±0.5	0.2±0.6	0.2±0.7	0.64
Total	5.9±2.4	4.5±2.3	5.8±2.9	0.11

Table 5. Comparison of RSI after 3 month treatment in all groups.

Parameter	NAS + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Hoarseness or a problem with voice	1.2±0.85	1.9±1.1	2.4±1.0	< 0.001*
Throat clearing	1.2±1.0	1.9±1.0	2.7±1.3	< 0.001*
Excess throat mucus or postnasal drip	1.2±1.2	1.8±1.1	3.2±1.2	< 0.001*
Difficulty swallowing food, liquids or pills	0.4±0.6	0.5±1.0	0.6±0.8	0.70
Coughing after you ate or lie down	0.7±1.1	0.7±0.9	0.7±1.1	0.95
Breathing difficulties or choking episodes	0.4±0.8	0.6±0.9	0.6±1.1	0.83
Troublesome or annoying cough	0.4±0.7	0.2±0.7	0.9±1.4	< 0.001*
Sensations of something sticking in your Throat or a lump in your throat	0.5±0.8	1.4±1.2	2.2±1.2	< 0.001*
Heartburn, chest pain, indigestion, or Stomach acid coming up	0.9±0.8	1.5±0.9	2.5±1.4	< 0.001*
Total	7.6±4.3	10.8±4.6	15.9±5.3	< 0.001*

Table 6. Comparison of RFS after 3 month treatment in all groups.

Parameter	NAC + Omeprazole	Omeprazole + Placebo	NAC + Placebo	*P*-value
Pseudosulcus	0.0±0.3	0.0±0.3	0.1±0.5	0.77
Ventricular obliteration	0.1±0.5	0.3±0.9	0.4±0.8	0.04*
Erythema and hyperemia of larynx	0.8±1.2	1.1±1.1	1.6±1.4	0.02*
Vocal cord edema	0.7±0.6	0.5±0.5	1.0±0.8	0.06
Diffuse laryngeal edema	0.1±0.4	0.1±0.3	0.5±0.9	0.04*
Post commissure hypertrophy	0.7±0.6	0.9±0.6	1.0±0.8	0.03*
Subglottic granuloma and granulation	0.0±0.0	0.0±0.0	0.0±0.0	-
Thick endolaryngeal mucus	0.3±0.5	0.2±0.6	0.2±0.6	0.6
Total	2.9±2.4	3.1±2.1	4.9±3.5	0.04*

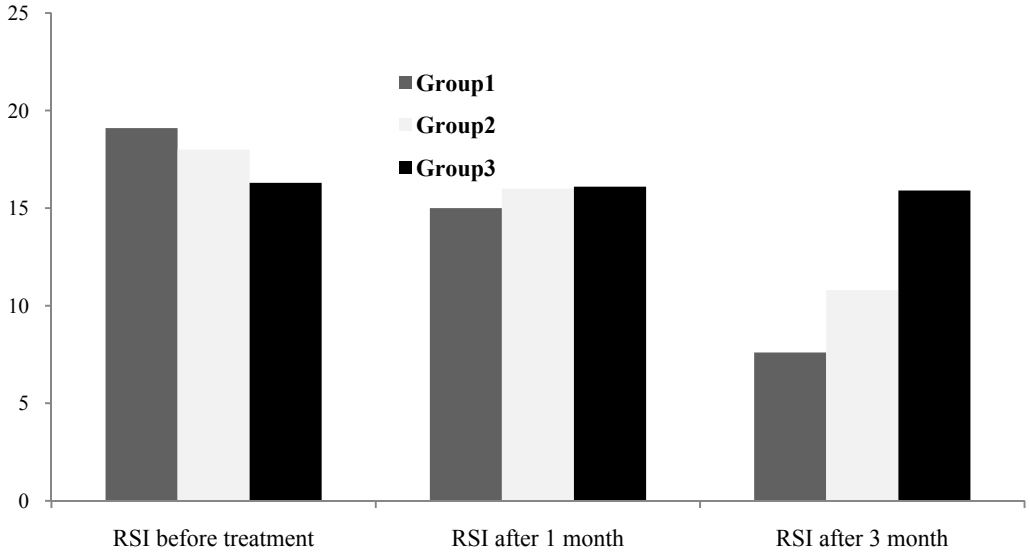

Figure 1. Comparison of RSI before and after treatment in all groups.

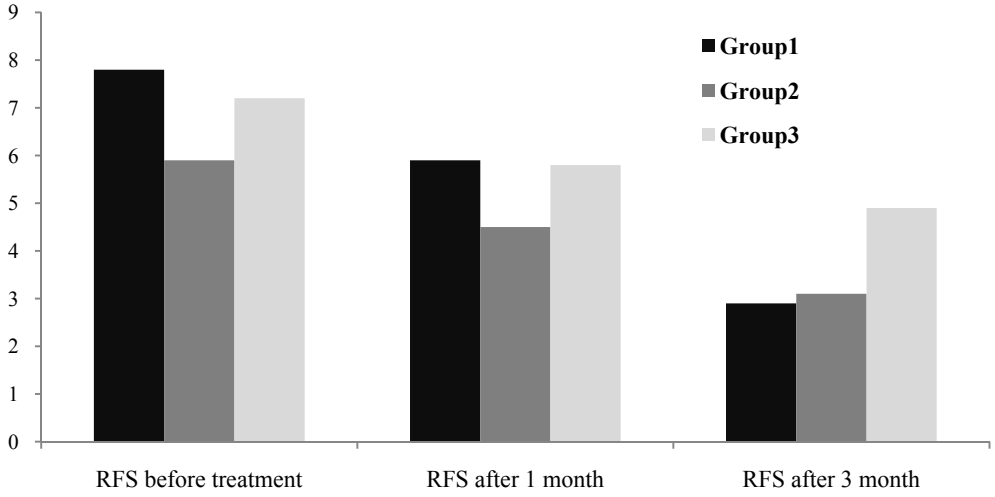

Figure 2. Comparison of RFS before and after treatment in all groups.

Overall on the basis of the results of this study, despite therapeutic efficacy of all treatment protocols, the RSI after 3 months was significantly different in (NAS+ Omeprazole) and (Omeprazole+ placebo) groups (P<0.001 in the first group, P<0.001 in the second group and P=0.35 in last group).

As shown in figures 1 and 2, there was significant difference in all groups in RFS before and after 3 months treatment (P<0.001 in each group in comparison with itself) but we did not find a significant difference after 1 month of treatment. Also our results showed that the most recovery can be seen in the first group in comparison with other groups.

Discussion

Retrograde movement of gastric contents in to the upper esophageal sphincter (UES) and respiratory system cause laryngeal inflammation (17-21). Several lines of evidence indicate that patients with GERD have an increased risk of developing concomitant laryngeal disorders (22-24) that two possible mechanisms have been proposed for this concomitant including direct injury by microaspiration of gastric contents into extra-esophageal structures during reflux episodes and stimulation by the gastric refluxate of a vagal reflex arc extending from the esophageal body to the

bronchopulmonary and laryngeal systems (25-29).

In addition to flexible or rigid laryngoscopy examination, and laryngeal sensory testing, LPR and GERD can be evaluated by several diagnostic tests including barium esophagography, radionuclide scanning, Bernstein acid perfusion test, esophagoscopy with biopsy, impedance testing, and pH probe monitoring.

Dual pH probe testing is reasonably sensitive and specific for reflux events, and is typically done in an outpatient setting with the patient being monitored over an 18- to 24-hour period. On the other hand the role of proximal esophageal pH monitoring in predicting response of laryngitis to acid-suppressive therapy is still poorly defined. Although the presence of acid reflux in the proximal esophagus might be suggestive for the presence of GERD-related laryngitis, its sensitivity and reproducibility are too low (55%) to be used as an initial diagnostic test for GERD-related laryngitis (30, 31).

The relative ease of administrating a PPI makes it an attractive initial therapy in managing suspected GERD-related laryngitis. Also several investigators suggested using the symptomatic response to high-dose PPI as a diagnostic tool for GERD (32,33) and GERD related extra-esophageal complications such as laryngitis (34), non-cardiac chest pain (35,36), and chronic cough (37,38).

In an interesting study, Seckin *et al*. examined the prognostic value of anti-reflux treatment in patients with posterior laryngitis and with or without pharyngeal reflux sign. This study reported medical anti-reflux treatment is effective for relief of symptoms (39).

In our study, also we showed that the use of Omeprazole as anti-reflux treatment is effective for the relief of the subjective and endoscopic findings. We also used NAC in comparison with Omeprazole. This drug is both a mucolytic and antioxidant which might have benefit in inflammatory airway diseases associated with mucus overproduction and maybe reduces the use of mechanical processes by disulfide bonding with mucin gel (40). In a study in 2011 in relation with effect of mucolytic drugs in treatment of patients with increasing discharge air ways, Guaifenesin in combination with this drug was introduced as a suitable composition (41).

But at the present there are only few studies about this drug and its role in treatment of laryngopharyngeal reflux. Therefore, this study we evaluated the effects of this drug in comparison with Omeprazole in treatment of LPR symptoms.

Our results from the NAC + placebo showed no significant differences in the questionnaire that was filled by the patients before and after treatment. Therefore, it can be concluded that this drug cannot be used alone to reduce of symptoms, although the objective signs had more statistically significant decrease with this drug.

In this study, as well as GERD-related laryngitis, patients treated with Omeprazole + placebo were satisfied more with this medication in comparison with NAC + placebo. In addition more improvement was obtained in the examinations after treatment (compared with patients treated with NAC)

Also, based on questionnaires and endoscopic finding, Omeprazole in combination with NAC had the most effectiveness and patients in this group had the most satisfaction of their medication in comparison with other medications.

In a case control study by Hopkins *et al*. in 2006, in relation with the treatment of hoarseness due to acid reflux conducted, 302 patients with laryngitis with unknown cause such as malignancy, paralyzed vocal cord or nodule with and without a diagnosis of GERD were enrolled. Anti-acid drug used in this study were from PPI group (Omeprazole) (42). At the end of this study, it was demonstrated that patients in control group had quantitative responding to treatment with placebo. This result showed that treatment in these patients was not dependent to anti-acid drug alone. The present study has similar results, the objective finding was better in 3 groups of patients in comparison with initial study. Although the results did not confirm by subjective signs.

On the other hand, the use of placebo allowed us to study all three groups in the same conditions, in terms of the psychological interaction with drugs. Eventually, the results of study indicate that patients will best respond to treatment when the anti-acid effects of Omeprazole placed along the mucolytic effect of NAC. In conclusion, our results showed that combination therapy with Omeprazole and NAC has the most effectiveness on both subjective and objective questionnaires at least after 3 months treatment. Also based on the results of present study, it seems that using of objective tools is more accurate than subjective tools in evaluation of therapeutic effects in patients with GERD-related laryngitis.

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