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Original Research Article

Combination drug therapy for laryngopharyngeal reflex

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ABSTRACT

Background: We sought to evaluate the combination of high-dose prebreakfast proton pump inhibitors (PPIs) (40 mg pantoprazole) and a bedtime high-dose ranitidine (300 mg) dosing as a surrogate and rational regimen for LPR.
Methods: 60 subjects that presented to ENT and HNS OPD with symptoms of laryngopharyngeal reflux (LPR) were prospectively evaluated and underwent a comprehensive otolaryngological examination. All subjects were treated sequentially and outcomes recorded using reflux finding score (RFS) and reflux symptom index (RSI).
Results: The mean age of the cohort was 35±06.51 (age range, 8-55). Mean RSI of all patients was 24.8 before treatment with combination of PPIs and H2 receptor antagonists. Significant change in RSI were observed after the first 8 weeks of therapy and no further significant changes were observed over the next 16 weeks. Mean RFS of the patients was 12 before starting the treatment and there was a significant response in mean RFS at 16 weeks of therapy.
Conclusions: A surrogate high-dose prebreakfast PPI (40 mg pantoprazole) and a bedtime high-dose ranitidine (300 mg) dosing regimen is effective in improving RSI and RFS in majority of cases who present with LPR.

Keywords: Laryngopharyngeal reflux, Gastroesophageal reflux disease, Reflux symptom index, Reflux finding score, Proton-pump inhibitors, H2 receptor antagonists

INTRODUCTION

Laryngopharyngeal reflux (LPR) is defined as irritation and inflammation of the laryngeal structures resulting from contact with gastric secretions. It is a very common condition and it has been recently distinguished as a separate, though related, entity from gastroesophageal reflux disease (GERD). Acid reflux diseases are highly prevalent and GERD and LPR are epidemic.[1-5]

The difference between the two entities was highlighted by James in 1991. James emphasized the otolaryngo-logical importance of reflux and described reflux as an underlying etiology in (40-60) % of patients with various voice disorders. LPR has been reported in up to 10% of patients presenting to an otolaryngologist office and 1% of patients to primary care physicians. James et al, estimated that 50% of all patients presenting with voice or swallowing disorder exhibit LPR.[6,7]

The symptoms reported in GERD and LPR have long been described. Hippocrates described globus pharyngeus over 2500 years ago. Heartburn was first described by Galen in 200 AD and observed that diseases of the esophagus mimicked those of the heart.[8] LPR can present with a myriad of symptoms, including hoarse voice, throat clearing, chronic cough, globus sensation, postnasal drip, dysphagia and sore throat.

Current understanding of LPR has come a long way since the first descriptions of symptoms. By the mid to late 1990s, the term laryngopharyngeal reflux started to be

used and in 2005, Ford published a systematic review that highlighted the unique symptom complex and pathophysiology of LPR.[9-11]

Belafsky et al have developed a self-assessment tool, the reflux symptom index (RSI), which could help clinicians assess the relative degree of LPR symptoms during initial evaluation and after treatment. Patients are asked to use a 0 to 5 points scale to grade the 9 items symptoms. An RSI of more than 13 is considered to indicate LPR. It ranges from 0 to 45 (worst possible score).[12]

Reflux finding score (RFS) is an 8 items clinical severity rating scale based on fiberoptic laryngeal findings. The scale includes most common LPR-related laryngeal findings and it was concluded that any person with RFS greater than 7 is more than 95% likely to have LPR.[13]

The pH-impedance monitoring which was until now the gold standard for the diagnosis of LPR is losing its credibility because it has many flaws such as the high-cost procedure and high rates of false positive and false negative.[14]

The laryngoscopic findings used for the diagnosis of reflux are non-specific signs of laryngeal irritation and inflammation. The laryngeal examination identifies edema and erythema, particularly in the posterior region. Besides that, according to some investigators, these findings are also seen in healthy subjects, and the type of endoscope can influence the color of erythema.[11]

Furthermore, because the examination depends on the examiner, variations may exist that make the precise diagnosis of LPR highly subjective.[15]

The management of LPR includes lifestyle and dietary modifications, medical and surgical treatments. LPR treatment requires acid suppression to be aggressive and for a prolonged period of time than GERD in view of the fact that only a small amount of acid reflux into the upper aerodigestive tract is capable of causing significant symptom and as such the recommended medical treatment is twice-daily-dose (BID) proton pump inhibitors (PPIs) for three to six months.[11,16]

The role of BID PPIs with or without the addition of an H2-receptor antagonist in the management of LPR has been previously evaluated in the literature. However very few studies have evaluated a simpler and less intensive acid suppression regimen that has been informally the initial treatment of choice for LPR of many otolaryngologists: one dose of 40 mg pantoprazole or equivalent before breakfast (BBF) and a bedtime (HS) dose of 300 mg of ranitidine or equivalent to provide 24 hours of acid suppression (BBF/HS dose).

By avoiding the second dose of PPI, one of the food-timing dependent dose of medication is eliminated; the potential cumulative side effects of PPIs are decreased, and hope for better compliance may be possible as both pills become part of the patient's morning and evening bathroom routine.

H2RAs are a form of anti-histamine that interfere with the signals that cause stomach acid to be produced. These medications are not as strong as PPIs, but are more effective during sleep and may decrease the occurrence of nocturnal acid breakthrough, which is a histamine related phenomenon. Some patients may require H2RAs to help control nighttime symptoms.[17]

Although there is some controversy regarding proton pump inhibitor efficacy, they are considered the mainstay of medical treatment of LPR. Unfortunately, not all patients respond as expected to PPIs. Some patients require higher doses of medication, a change in their PPI, addition of H2RA or anti-reflux surgery to control LPR.[18]

Combination of PPI and H2RAs has been used for the treatment of patients with LPR in many studies. Some studies demonstrated clinically evident benefits in the treatment but some studies did not report any clinical benefits of the use of H2RA in LPR.[19-22]

There are very few studies that have studied the effects of combination therapy with PPI and H2RA (BBF/HS dose) in patients with LPR. The objective of this study was to evaluate once-daily, 40 mg pantoprazole and once nightly, 300 mg ranitidine (BBF/HS) dosing as an alternative empiric regimen in the management of LPR. To the best of our reviewed knowledge no study exists in the indexed literature that has studied the effects of combination therapy in the management of LPR in our demographic setup.

METHODS

This prospective observational study was conducted in the Department of ENT and Head and Neck surgery, Government Medical College, Srinagar, India for a period of 2 years from June 2017 to May 2019.

A total of 72 patients diagnosed with LPR and who met the selection criteria were enrolled in this study. 12 patients were lost to follow up. Reflux symptom index and reflux finding score were used to diagnose LPR.

Inclusion criteria

Inclusion criteria includes patients of any age group, reflux symptoms index (RSI) 13 or more and reflux finding score (RFS) 7 or more.

Exclusion criteria

Exclusion criteria includes patients who had laryngeal malignancy or vocal fold mass, or history of previous gastrointestinal tract surgery, patients with history of anti-reflux medication in the preceding one month, with RFS

less than 7 and/or RSI less than 13, pregnant patients or on breast feeding and psychiatric patients.

Procedure

A detailed history including onset, duration and associated symptoms was obtained from the patients. The patients were subjected to thorough ENT examination including flexible fiberoptic laryngoscopy, which was performed in all cases. The diagnosis of LPR on first visit was done on the basis of symptom scoring called reflux symptom index and laryngoscopic findings called reflux finding score (Table 1 and 2).

Table 1: Reflux symptom index.

Complaint	Yes/no	Duration
Hoarseness or problem with voice	-	-
Frequent clearing of throat	-	-
Excess throat mucus or postnasal drip	-	-
Difficulty swallowing food, liquids or pills	-	-
Coughing after having eaten or after lying down	-	-
Breathing difficulties or chocking episodes	-	-
Troublesome or annoying cough	-	-
Sensations of something sticking in throat or a lump in throat	-	-
Heartburn, chest pain, indigestion or stomach acid coming up	-	-

Table 2: Reflux finding score.

Pseudosulcus	0-absent, 2-present
Ventricular obliteration	0-none, 2-partial, 4-complete
Erythema/hyperemia	0-none, 2-arytenoid only, 4-diffuse
Vocal cord edema	0-none, 1-mild, 2-moderate, 3-severe, 4-obstructing
Diffuse laryngeal edema	0-none, 1-mild, 2-moderate, 3-severe, 4-obstructing
Posterior commissure hypertrophy	0-none, 1-mild, 2-moderate, 3-severe, 4-obstructing
Granuloma/granulation	0-present, 2-absent
Thick endolaryngeal mucus	0-absent, 2-present

Each patient was put on once a day PPI therapy (before breakfast). PPI used in the study was pantoprazole 40 mg. Patients were also put on H2RA ranitidine 300 mg at bedtime.

There were 16 weeks of follow up to each patient. Fiberoptic laryngoscopic evaluation was performed twice: first at 8 weeks, then at 16 weeks. On each of these visits, RFS and RSI were administered. Effect of combination of PPI and H2RA on reflux finding score and reflux symptom index at each follow up visit was used to assess the success of therapy. The paired sample t-test was used to evaluate the difference between reflux symptoms and findings at each treatment follow-up.

Data was entered in a Microsoft Excel spreadsheet and analysed using SPSS v23 and expressed as percentage. The paired sample t test was used to evaluate the difference between reflux symptoms and findings at each treatment follow-up. Two-tailed p values were reported and a $p<0.05$ was considered statistically significant.

RESULTS

Total number of patients included in the study were 60, 35 (58.3%) cases were females and 25 (41.6%) were males. Male to female ratio in the study was 1:1.4. Age of the patients varied from 8 to 55 years. Maximum numbers of patients were in the age group 31 to 40 years forming about 45% of the study group population. Mean age of the study population was 35 years.

Table 3: Percent distribution of symptoms (RSI).

Symptoms	No. of patients	Percentage (%)
Hoarseness	17	28.3
Foreign body sensation in throat	41	68.3
Difficulty in swallowing	37	61.6
Difficulty in breathing	13	21.6
Nocturnal cough	23	38.3
Frequent throat clearing	36	60
Pain in throat	18	30
Heartburn/palpitations	21	35

Foreign body sensation in throat (Table 3) was the most common symptom present in 68.3% of patients followed by difficulty in swallowing in 61.6% and frequent throat clearing in 60% of patients.

Mean RSI of all patients was 24.8 before starting the combination therapy with proton pump inhibitors and H2RA. After 8 weeks of therapy mean RSI decreased to 12.6 and after 16 weeks of combination therapy mean RSI dropped to 12 (Table 4) which was statistically significant.

Table 4: Change of RSI with combination therapy.

Age group (in years)	No. of patients	Pre-treatment (RSI)	Post-treatment (RSI) at 8 weeks	Post-treatment (RSI) at 16 weeks
0-10	0	-	-	-
11-20	7	23	11	11
21-30	12	25	14	13
31-40	27	27	12	12
41-50	10	25	13	11
51-60	4	24	13	13
Total	60	24.8	12.6	12

Table 5: Percentage distribution of signs (RFS).

Findings	No of patients	Percentage (%)
Pseudosulcus	28	46.6
Erythema/hyperemia	45	75
Diffuse laryngeal edema	32	53.3
Ventricular obliteration	39	65
Vocal fold edema	30	50
Granulations/granuloma	20	33.3
Posterior commissure hypertrophy	39	65
Thick endolaryngeal mucus	20	33.3

Significant change in RSI was observed after first 8 weeks of therapy in all age groups and very little appreciable improvement was seen over the next 8 weeks.

Most common laryngeal finding (Table 5) was erythema/hyperemia which was observed in 75% of subjects, followed by ventricular obliteration and posterior commissure hypertrophy in 65% of subjects each. Mean RFS of the patients was 12 before the start of combination therapy with PPI and H2RA. After 8 weeks of combination therapy mean RFS decreased to 9.8 and after 16 weeks of combination therapy mean RFS dropped to 6.8 (Table 6) which was statistically significant. There was appreciable response after 8 weeks of therapy in physical findings in all age groups but significant response was observed after 16 weeks of therapy in all age groups.

Table 6: Change of RFS with combination therapy.

Age group (in years)	No. of patients	Pre-treatment RFS	Post-treatment RFS at 8W	Post-treatment RFS at 16W
0-10	0	-	-	-
11-20	7	11	9	7
21-30	12	11	9	7
31-40	27	13	10	6
41-50	10	13	11	6
51-60	4	12	10	8
Total	60	12	9.8	6.8

DISCUSSION

LPR has become a common disease presenting to an otolaryngologist. Over the past few years, an increasing number of studies have been published in the medical literature on management of LPR, but there are still controversies in its treatment.[23] The optimal treatment of LPRD is neither standardized nor validated.[24]

In contrast to what is seen in GERD, the response to treatment with PPIs varies widely among patients with LPR. Some authors believe that treatment of LPR requires higher doses and longer treatment when compared with GERD.[22] The recommendation is that empirical therapy should use the full dose of PPIs for a minimum period of 2 to 3 months.[1,16] Combination of PPI and H2 receptor antagonists has been used for the treatment of patients with GERD in many studies but the role of H2RAs in management of LPR has not been thoroughly evaluated.[11,20]

H2 receptor antagonists are a form of anti-histamine that interfere with the signals that cause stomach acid to be produced. These medications are not as strong as PPIs, but are more effective during sleep. H2 receptor antagonists have a role to play in patients who suffer from nocturnal acid breakthrough despite twice-daily PPI therapy, or for long-term management of reflux symptoms on an 'as needed' basis.[25,26]

With careful studies, it has become clear that at least 70% of patients (or normal subjects) will continue to secrete acid and decrease their intragastric pH to less than 4 for at least 1 hour overnight despite twice-daily PPI therapy. This phenomenon, termed nocturnal gastric acid breakthrough (NAB), usually occurs about 6±7 hours after the evening dose of the PPI, principally between 1 and 4 am and is believed to be a histamine-related phenomenon; and it is this phenomenon that makes these patients a suitable target for add on H2RA therapy in combination with PPIs.[27]

Moreover, compliance with BID dosing that requires timing with meals and concern for emerging and more numerous side effects from PPIs has led many to question the practice of offering empiric PPI trials.[28,29]

In addition, PPI therapy for treatment of LPR has also been criticized because PPI therapy is based on a poor level of evidence.[30] It should also be acknowledged simultaneously that the addition of H2RAs to BID PPIs has been suggested earlier and is controversial.

The purpose of our study was to report our experience on the role of combination therapy with PPIs and H2RAs in the management of LPR by observing the effects on RFS and RSI. This study presents a surrogate dosage regimen that is more compliant to the patient and also reduces the exposure to PPIs.

In our study, maximum numbers of patients were in the age group 31 to 40 years forming about 45% of the study group. Gender wise females accounted for 58.3% of the study population. Female predominance was also seen in the studies of Issing et al, Bilgen et al, Mesallam et al, and Toros et al.[31-34]

Empiric once-daily, high-dose prebreakfast PPI (40mg pantoprazole) and a bedtime high-dose ranitidine (300mg) has not been thoroughly evaluated for effectiveness in the treatment of LPR in the literature despite its anecdotal use. Our study demonstrated a significant improvement in both RSI and RFS for all age groups and in total, at 8 weeks and 16 weeks of follow up and the results were statistically significant. This is a rate similar to prior reports of other regimens.[20]

Laryngeal signs took 4 months to show improvement, and only after 4 months of therapy did RFS decrease significantly. These results were comparable to a similar study conducted by Carroll et al, which demonstrated that a once-daily, 40 mg omeprazole and once nightly, 300 mg ranitidine (QD/QHS) dosing improved the majority (67%) of patients who presented with signs and symptoms of LPR and ultimately responded to empiric acid suppression.[19]

Although similar results have been demonstrated in studies of Belafsky et al.[12] and Bilgen et al.[32] but these studies used pH monitoring for diagnosis of LPR and used only PPIs in the treatment of LPR. pH monitoring was not done in our study. Patigaroo et al, have also generated identical results in their study conducted with identical selection criteria but again in this study only empiric PPI BID dosing was used.[35]

Drugs that require more frequent dosing have notoriously lower adherence rates.[28] 2000 Gallop study found that only 46% of patients on BID PPIs took them correctly. Thirty-one percent took the evening PPI at bedtime rather than before their evening meal, and 4% simply took the second PPI dose as needed.[36] The dosing regimen employed in our study is easier to adhere to, and because it requires one less pill to be timed prior to meals ensures better compliance.

Although there is significant improvement in RFS and RSI at 16 weeks follow up and patients are symptom free, but treatment should be continued for at least 6 months. Consensus conference report 1997 on LPR opined similarly and suggested that twice-daily PPI treatment is to be continued for a minimum of 6 months.[37]

The current research indicates that the majority of patients will respond to a single daily dose of PPI and a bedtime dose of H2RA provided the acid suppression therapy works. This dosing regimen will also improve compliance and therefore improve treatment outcomes. In addition, owing to the concerns regarding negative side effects of high-dose PPIs, starting with this dosing regimen may be a reasonable first treatment step in the management of LPR.

We can safely conclude that while many studies are still needed to evaluate optimal therapeutic management of LPR, it is recommended that a multidisciplinary approach including ENT, pulmonology and gastroenterology evaluations be employed to improve diagnosis and therapy for LPR patients.

CONCLUSION

Otolaryngologists frequently encounter LPR in their office. The RFS and RSI developed by Belafsky et al, are useful tools for diagnosing LPR and for monitoring the treatment. Despite the controversies, a common, initial therapy for suspected LPR remains empiric acid suppression with BID PPIs. This study demonstrated that a once-daily, high-dose prebreakfast PPI (40mg pantoprazole) and a bedtime high-dose ranitidine (300 mg) regimen results in symptomatic improvement in majority of patients who present with signs and symptoms of LPR. Our study demonstrated a significant improvement in both RSI and RFS for all age groups. In view of concerns about the negative side effects of PPIs and the known compliance difficulty associated with second dose of predinner PPI, the present study suggests that the once-daily, high-dose prebreakfast PPI (40mg pantoprazole) and a bedtime high-dose ranitidine

(300mg) dosing scheme may be considered as a rational alternative for empirical treatment in patients with LPR.

Nonetheless, more studies are needed to identify patient subgroups with LPR symptoms that would benefit from this dosing regimen.

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