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Original Research Article

Study of the empirical role of proton pump inhibitor therapy on laryngopharyngeal reflux

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ABSTRACT

Background: Laryngopharyngeal reflux (LPR) is a highly prevalent disease and commonly encountered in the otolaryngologist's office. Study to evaluate the presentation of different signs and symptoms of LPR along with evaluating the role of empiric PPI (proton pump inhibitor) in the management of LPR by observing its effect on RFS and RSI.
Methods: A prospective observational study was conducted on 100 cases having different symptoms of LPR. Reflux symptom index (RSI) and Reflux finding score (RFS) were used to diagnose LPR. Patients were put on PPI (Pantoprazole 40 mg OD for 12 weeks) and followed up at 4,8 and 12 weeks and successive RSI and RFS scores were evaluated. The results were compiled and analyzed statistically.
Results: Among all symptoms, most common presenting symptom of LPR was foreign body/sensation of something sticking in throat (80%). Upon pharmacological therapy with PPIs (Pantoprazole), the mean RSI score changed from 22.94±5.83 to 11.19±2.97 at 12 weeks of PPI therapy. The mean RFS score changed from 12.93±3.55 to 6.86±2.86 at 12 weeks of PPI therapy. The change in the RFS and RSI score was highly significant (p=0.001).
Conclusions: LPR is a common condition presenting in ENT settings, the symptoms and signs of which may be complex. RFS and RSI score are valuable tools for diagnosing LPR. PPIs are proven to be effective therapy for LPR, more studies are encouraged to affirm the efficacy of PPIs over other management options.

Keywords: LPR, PPI, RFS, RSI

INTRODUCTION

Laryngopharyngeal reflux (LPR) is a highly prevalent disease and commonly encountered in the otolaryngologist's office. It is defined as the retrograde flow of stomach content to the larynx and pharynx whereby this material comes in contact with the upper aerodigestive tract.[1] It has been estimated that patients with LPR make up 4 to 10% of all patients seen in otolaryngology clinics.[2] In the esophagus, 50 reflux episodes per day are considered to be normal, whereas in the larynx even three episodes can cause harm.[3] Apart from acidic reflux, nonacid reflux has also been associated with inflammation in both LPR and GERD, indicating that reflux components such as pepsin and bile salts can also cause mucosal damage.[4]

The most common symptoms of LPR are excessive throat clearing, coughing, hoarseness, and globus pharyngeus ("lump in the throat sensation"). Belafsky et al developed a nine-item questionnaire RSI for the assessment of symptoms in patients with reflux disease that can be completed in less than 1 minute.[5] The scale for each individual item ranges from 0 (no problem) to 5 (severe problem), with a maximum score of 45 (Table 1) and RSI score >13 defined as abnormal.

LPR has been implicated in the etiology of many laryngeal diseases such as reflux laryngitis, subglottic stenosis, laryngeal carcinoma, granulomas, contact ulcers, and vocal nodules. Patients with LPR may endure prolonged and exhaustive suffering because of its non-specific signs and symptoms and as they can be manifestations of other etiologies, such as infection, vocal abuse, allergy, smoking, irritant inhalation, heavy drinking, or non-pathologic alterations.[2,5]

In an attempt to identify the most specific laryngoscopic signs of LPR, Belafsky et al developed the RFS based on the findings of fiberoptic laryngoscopy. This scale evaluates eight items that comprise the most common laryngoscopic findings (Table 2) in patients with LPR. Each item is scored according to severity, location, and presence or absence, for a total score of 26. Patients presenting a score of 7 or higher are classified as having LPR.[6]

It should be emphasized, however, that a thorough medical history and laryngoscopy are important for the proper workup of cases of LPR, precisely because there is no gold standard for diagnosis. Treatment of LPR consists of dietary changes and changes in habits such as weight loss, quitting smoking, avoiding alcohol, avoiding eating immediately before bedtime and dietary restrictions.[7] At present, the drugs most commonly used for the treatment of LPR are proton pump inhibitors (PPIs), which suppress acid production by directly acting on the H+-K+ ATPase of parietal cells, reducing the damage resulting from the enzymatic activity of pepsin, which requires an acid medium for activation.[8] They are prodrugs which require activation in an acid environment. Five PPIs currently widely available are esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.[9] Once-daily dosing in the morning is more effective than dosing in the evening for all PPIs with respect to the suppression of intragastric acidity and daytime gastric acid secretion in particular.[10]

The therapeutic response of patients with LPR to PPIs is variable, in part because LPR requires more aggressive and prolonged therapy than GERD.[11] Although most patients show improvement of symptoms within 3 months, the resolution of symptoms and laryngeal findings generally takes 6 months.[7] We here conducted a prospective study on 100 cases to study the presentation of different signs and symptoms of LPR along with evaluating the role of empiric PPI (Pantoprazole 40 mg OD) in the management of LPR by observing its effect on RFS and RSI.

METHODS

The present prospective observational study was conducted in the Department of ENT, Rajindra Hospital, Patiala from December 2014 to December 2016. A total of 100 cases having different symptoms of LPR fulfilling the criteria were included in the study. Sample size was calculated using:

$n=Z^2_{(1-\alpha/2)}*SD^2/(d)^2$

n=Sample size; Z=1.96; d=4; SD=20. Thus minimum=96 sample are required for the study.

RSI (Table 1) and RFS (Table 2) were used to diagnose LPR. Each patient underwent examination comprising detailed history, physical examination to exclude other causes, indirect laryngoscopy, rigid video laryngoscopy using 70-degree rigid endoscope. The diagnosis of LPR was made on first visit on the basis of symptom scoring (RSI) and laryngoscopy findings (RFS). Patients were put on PPI (Pantoprazole 40 mg OD for 12 weeks) and followed up in OPD for 12 weeks on three occasions at 4,8 and 12 weeks and successive RSI and RFS scores were evaluated.

Patients included were of age group 18-70 years, of any sex with symptoms of LPR for last 1 month and with both RSI>13 and RFS>7. Patients who were willing to participate were enrolled in the study.

Patients excluded were, with some other obvious cause of symptoms and signs like malignancy, with history of PPI intake in the preceding month, patients with RFS less than 7 and/or RSI less than 13 or those who refused for the surgery.

The patients were asked to fill questionnaire form for RSI score and laryngeal endoscopy was done for RFS initially and at 4-, 8- and 12-weeks post PPI treatment. Results of demographic characteristics and other parameters were expressed as mean ± standard deviation. All parameters were compared using paired t test. The results were compiled and analyzed statistically.

RESULTS

In our study the mean age of presentation of patients was 42.91 (±9.64) years. 50% of the cases were in between 41-50 years of age whereas 19% were ≥51 years,16% were 31-40 years and 15% were ≤30 years of age. Maximum number of LPR cases was seen in 41-50 years of age (50%). Out of 100 patients, 42% of the patients were males while 58% were females. So male: female ratio was 2:3 indicating a female preponderance.

The most common presenting symptom of LPR was foreign body/sensation of something sticking in throat (80%) followed by throat clearing (68%), difficulty in swallowing food/ liquids (65%), heartburn/ chest pain/ pain indigestion (55%), coughing after eating or lying down (54%). The most common sign of LPR was erythema/hyperemia (88%) followed by posterior commissure hypertrophy (86%), ventricular obliteration (82%), diffuse laryngeal edema (53%), vocal cord edema (52%) and pseudosulcus (50%).

Upon pharmacological therapy of LPR patients with PPIs (Pantoprazole), the mean RSI score changed from 22.94±5.83 to 16.67±5.43 at 4 weeks of PPI therapy, to 12.20±3.94 at 8 weeks of PPI therapy and to 11.19±2.97 at 12 weeks of PPI therapy. The largest change in the mean RSI score was seen at 4 weeks of therapy. The change in the RSI score was highly significant (p=0.001).

The mean RFS score changed from 12.93±3.55 to 10.81±3.20 at 4 weeks of PPI therapy, to 8.67±3.42 at 8 weeks of PPI therapy and to 6.86±2.86 at 12 weeks of PPI therapy. The change in the RFS score was highly significant (p=0.001) at all the time points.

Table 1: Reflux symptom index.

Within the last month, how did the following problems affect you?	0=no problem, 5=severe problem					
Hoarseness or **a problem with your voice**	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucous or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations or something sticking in your throat	0	1	2	3	4	5
Heart burn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

Table 2: Reflux finding score.

Variables	Score
Pseudosulcus	0 absent, 2 present
Ventricular obliteration	0 none, 2 partial, 4 complete
Erythema/ hyper-anemia	0 none, 2 arytenoids only, 4 diffuse
Vocal cord edema	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing (polypoidal)
Diffuse laryngeal edema	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing
Posterior commisure hypertrophy	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing
Granuloma/ granulation	0 present, 2 absent
Thick endolaryngeal mucus	0 absent, 2 present

DISCUSSION

Gastroduodenal content reflux can directly or indirectly lead to an inflammatory disorder of the upper aerodigestive tract tissues known as LPR, which can induce morphologic changes in the above tract.[12] Over the last decades, there has been increase in the number of medical visits because of reflux, either LPR or gastroesophageal reflux disease (GERD), and the corresponding increase in the number of anti-reflux prescriptions.[13]

Reflux has been shown to be associated with subglottic stenosis, laryngospasm, obstructive sleep apnea, bronchiectasis, and rhinitis or chronic rhinosinusitis.[7] Thus, Belfasky et al developed simple non-invasive, economical instruments RSI and RFS to help in the diagnosis of LPR. RFS is an 8-item clinical severity rating scale based on laryngoscopic findings and it has been concluded that any individual with RFS greater than 7 has more than 95% probability of having LPR. RSI on the other hand is a 9-item self-administered outcome instrument. An RSI of more than 13 is considered to indicate LPR. [5]

It has been seen that response to empiric treatment with PPI is a more common and acceptable initial diagnostic strategy for uncomplicated LPR. As such, we decided to assess LPR-related symptoms and signs with the use of RSI and RFS score accompanied by efficacy of PPI (pantoprazole) in management of LPR.

In the present study overall maximum prevalence of LPR was seen from 4th to 6th decade with peak incidence in 4th decade. The mean age of presentation of patients was 42.91 (±9.64) years. This was comparable with study conducted by Somashekhra et al which reported that the mean age of patients of LPR to be 42.7 years.[14] Another study conducted by Patigaroo et al reported the mean age of patients of LPR to be 38 years.[15]

In our study there were 58 females and 42 males and male: female ratio was 2:3. Our study is in concordance with the study conducted by Patigaroo et al which showed that 60% of LPR cases to be females while 40% were males (male:female-2:3).[15] According to our study, the most common presenting symptom of LPR was foreign body/Sensation of something sticking in throat (80%) followed by throat clearing (68%), difficulty in swallowing food/liquids (65%), heartburn/ chest pain/pain indigestion (55%), coughing after eating or lying down (54%). The results of our study are comparable with the results of the study conducted by Kavitha et al which reported the most common symptom to be frequent clearing of throat (98%) followed by sensation of lump in throat and troublesome cough (96% each).[16] The less common symptoms were post nasal drip/excessive throat mucous (80%), heartburn/chest pain/indigestion (76%) and hoarseness of voice, dysphagia (66%), cough after eating (56%) and dyspnea/choking (38%).

Another study conducted by Somashekhra et al reported the most frequent symptom to be persistent cough (86.6%) and globus sensation (85%) followed by throat pain (80%).[14] Difficulty in swallowing was found in 45% of the cases, throat clearing in 55%, hoarseness of voice in 30% and heartburn in 35% of the cases.

However, Koufman et al in his landmark study found that hoarseness of voice was present in 71% of cases followed by cough in 51% globus in 47% and throat clearing in 42% of cases.[2] The results are different from our study which might be attributed to the fact that RSI was not used to grade symptoms in their study.

In the present study, the most common clinical findings in the patients of LPR were erythema/hyperemia (88%), posterior commissure hypertrophy (86%) and ventricular obliteration (82%). Other findings included diffuse laryngeal edema (53%), vocal cord edema (52%), pseudosulcus (50%), thick endolaryngeal mucous (44%) and granuloma/granulation (41%). The present study was comparable to study conducted by Patigaroo et al which reported that the most common signs in the patients of LPR were erthema/hyperemia (88%), posterior commissure hypertrophy (60%) and ventricular obliteration (76%). Other findings were diffuse laryngeal edema (52%), vocal cord edema (52%), pseudosulcus (50%), thick endolaryngeal mucous (40%) and granuloma/granulation (40%).[15] Another similar study conducted by Kavitha et al found the most common laryngoscopic sign to be erythema/hyperemia in 84% of the patients followed by diffuse laryngeal edema in 82% of patients, posterior commissure hypertrophy (56%) and vocal cord edema (59%). Other less common findings were thick endolaryngeal mucous (38%), granuloma/ granulation (24%), ventricular obliteration (22%) and subglottic edema (14%).[16]

The results of present study were in discordance with the study conducted by Iqbal et al which reported the most common finding as vocal cord edema (97.1%) followed by hyperemia/erythema (93.3%), diffuse laryngeal edema (87.6%), posterior commissure hypertrophy (79%) and thick endolaryngeal mucus (65.99%).[17]

The specific reflux related mechanisms leading to LPR signs and symptoms are currently unknown and moreover problem of intra and inter observer variability prevails. It has been noted that correlations between laryngeal findings and symptoms are weak i.e., the findings normally associated with LPR may also be found among healthy controls, even as high as 86% as reported by Hicks et al.[18]

The meta-analysis by Wei pooled the results of 13 RCTs and has demonstrated a superiority of the PPIs over placebo for the treatment of LPR symptoms, as measured by the RSI.[5] Another study by Kavitha et al has reported the improvement of RSI from a pretreatment value of 16.50±1.66 to post treatment (PPI therapy) value of 11.94±1.79 after 4 weeks, 9.12±2.00 at 8 weeks and 5.44±2.08 at 24 weeks of treatment. There was improvement of RFS from a pretreatment value of 8.12±0.96 to post treatment (PPI therapy) value of 6.60±0.67 after 4 weeks, 5.22±0.79 at 8 weeks and 4.34±0.75 at 24 weeks of treatment which was statistically significant.[16]

The present study found that the mean RSI score changed from 22.94±5.83 to 16.67±5.43 at 4 weeks of PPI (Pantoprazole-40 mg OD) therapy, to 12.20±3.94 at 8 weeks of PPI therapy and to 11.19±2.97 at 12 weeks of therapy. The change in the RSI score was highly significant (p=0.001). The mean RFS score changed from 12.93±3.55 to 10.81±3.20 at 4 weeks of PPI (pantoprazole)therapy, to 8.67±3.42 at 8 weeks of PPI therapy and to 6.86±2.86 at 12 weeks of PPI therapy with highly significant p value.

Similarly, Wo et al evaluated the therapeutic effects of pantoprazole 40 mg (in the morning) in 20 patients and 19 controls who were followed for 12 weeks. Both groups experienced a statistically significant improvement in laryngeal symptom score.[19]

Likewise in a study conducted by Eherer et al where 21 patients were included in the study, both pantoprazole and placebo therapy resulted in a marked improvement in laryngitis scores and symptoms. While all 10 patients improved in the group receiving pantoprazole in the first round, placebo given as the first drug likewise led to objective improvement in 6/10. Pantoprazole resulted in a slight but statistically significant further improvement of laryngeal scores when it was given after placebo.[20]

Similarly in a study conducted by Semmanaselvan et al pretreatment RFS score of 12.62±1.48 significantly decreased to 1.74±1.24 at day 30 of fixed dose combination therapy of rabeprazole and domperidone. This value further decreased to 0.30±0.51 at day 90 of the therapy. There was a 46.82% reduction in RSI score at day 30 and 86.86% reduction at day 90.[21]

However, Eherer et al performed a crossover trial of pantoprazole 40 mg in 14 patients who were followed for 3 months. No statistically significant difference in improvements

in esophageal symptom scores and laryngeal symptom scores or in laryngeal examination findings were found between the pantoprazole and placebo regimens. The inconclusive evidence of PPI efficacy for LPR may reflect the possible multifactorial nature of the pathogenesis of the disease.[20]

Thus, from our study we observed that therapy with PPI is necessary for resolution of the physical findings in patients of LPR. In addition to the type of treatment and dosing, length of treatment is also of concern. LPR should be suspected when the history and laryngoscopy findings are suggestive of the diagnosis and the management should be multidisciplinary.

Limitations of this study could be lack of control group and the lack of comparison between the applied method and a method with higher specificity (flexible endoscopy or ambulatory 24-h double-probe pH monitoring). So, further studies with larger sample size, longer duration and multi-centric nature are warranted.

CONCLUSION

To conclude in nutshell, although LPR is a common condition presenting in ENT settings, the symptoms and signs may be complex. The RFS and RSI of Wake Forest University are valuable tools for diagnosing LPR as used in our study. PPIs are proven to be effective therapy for LPR, more studies are encouraged to affirm the efficacy of PPIs over other management options.

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