Laryngopharyngeal Reflux Disease - Do Prokinetic Drugs have any Role in Management?

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Abstract

Objective:
1. To diagnose laryngopharyngeal reflux disease (LPRD) clinically with the available subjective screening protocols (Reflux Symptom Index and Reflux Finding Score) to categorize the disease based on its severity.
2. To evaluate the role of Prokinetic drugs in the treatment of LPRD as a whole & in different disease severity groups.

Methods: A hospital-based interventional study was performed for a period of 5 months in patients presenting with symptoms suggestive of LPR in the outpatient department of R G Kar Medical College. The history was taken in detail and symptom scoring was done in terms of REFLUX SYMPTOM INDEX. Then fiber-optic laryngoscopic assessment was done in each patient and REFLUX FINDING SCORE was obtained. Reflux Finding Score over 7 was considered to be suggestive of LPR. The patients were then categorized to three severity groups. In each group, patients were randomly assigned to be treated with either pantoprazole with domperidone or with pantoprazole only. They were followed up at 1 & 3 months from initiation of treatment & assessed for improvement by using same criteria, RSI & RFS.

Results: High female preponderance was noted for LPR. Mostly the middle aged (30-50 years) persons were affected. Disease severity was almost the same in both sexes but symptom scores were much higher in females, particularly in extremes of ages. The commonest presenting symptom of LPR was found to be lumpy or sticky sensation in throat and common signs were laryngeal erythema, edema & posterior commissure hypertrophy. Laryngeal erythema was not found to be a reliable marker of disease severity but laryngeal edema & posterior commissure hypertrophy were. Focal vocal fold edema was a more consistent marker of disease severity than diffuse edema, especially in lower symptom group. Addition of prokinetic drugs in the management of LPRD was found to be satisfactorily effective. In refractory cases, reflux induction diet was prescribed, which worked quite well.

Conclusions: Prokinetic drugs are effective adjunct to pantoprazole in the management of LPRD.

Key Words: Laryngopharyngeal reflux; RFS; Prokinetic drugs; Induction reflux diet.

Introduction: Laryngopharyngeal reflux (LPR) is a controversial, high-frequency disease, and it differs from classic gastroesophageal reflux disease (GERD) in many ways. Typically, patients with LPR have daytime (upright) reflux without having heartburn or esophagitis. The threshold for laryngeal tissue damage is much lower than that for oesophagus; as many as 50 reflux episodes (less than pH 4) per day are considered normal for esophagus, whereas as few as 3 reflux episodes per week are too many for the larynx. However, though ambulatory 24-hour double-probe (simultaneous esophageal and pharyngeal) pH monitoring is the current gold standard for the diagnosis of LPR, pH-metry is not readily available in most of the institutions in India. Therefore, it is essential to clinically diagnose LPR accurately & institute appropriate treatment. In this study, an attempt has been made to find out the appropriate treatment - the role of prokinetic drugs in the treatment of LPRD.

Materials and Methods: A hospital-based analytical study was performed for a period of 5 months, from July 2013 to November 2013 in patients presenting with symptoms suggestive of LPR, attending the ENT outpatients' department (OPD) of R. G. Kar Medical College and Hospital, a tertiary care teaching institution in eastern India. The investigators, serving member of the unit had alternate day duty roster in the OPD during the given period. With prior administrative approval, the data was collected prospectively by interview and clinical examination. All the patients presenting within that period with laryngeal complains (like changes in voice, lumpy or sticky sensation in throat, difficulty in
swallowing, chronic cough, excess throat mucus and breathing difficulty) were first clinically examined including indirect laryngoscopy. The patients, who had no definite findings attributing to their symptoms (like neck mass including laryngeal tumors, thyroid enlargement and vocal nodules) were included in the study. Exclusion criteria were habit of smoking or tobacco-chewing, recent history of upper respiratory tract infection, history of any systemic inflammatory disease and voice abuse. A total of 108 patients were included in the study. After obtaining informed verbal consent from each of the patients, they were interviewed with predetermined questionnaire of REFLUX SYMPTOM INDEX (Table 1). Then Fibre optic laryngoscopy was done in each of the patients and REFLUX FINDING SCORE (Table 2) was obtained. A RFS score above 7 was considered suggestive of LPR. Data was analyzed for age & sex distribution. Both male & female were divided in 3 age groups - less than 30 years, 30 to 50 years & above 50 years. In each group, mean RSI & RFS were obtained & correlated between same age groups. Then different presenting symptoms & signs were analyzed for their relative percentage. The study population was then divided into 3 groups based on RSI score (group A : score below 15, group B : score 15-20, group C : score above 20). In each group, the mean value of different signs were calculated & analyzed for their correlation with disease severity. Finally the study population were divided into 3 groups based on RFS score ( 8 to 10, 11 to 14 & above 14). In each group, patients were randomly assigned to two groups- one to be treated with pantoprazole & domperidone combination capsules and the other with pantoprazole only. All patients were thoroughly counselled for lifestyle modifications.

Table 1: Reflux Symptom Index

Within the last month, how did the following problems affect you?

1. Hoarseness or a problem with your voice
2. Clearing your throat
3. Excess throat mucus or postnasal drip
4. Difficulty in swallowing food, liquids or pill
5. Coughing after you ate or after lying down
6. Breathing difficulties or choking episodes
7. Troublesome or annoying cough
8. Sensation of something sticking in your throat or a lump in your throat
9. Heartburn, chest pain, indigestion or stomach acid coming up

Each of the symptoms are graded from 0 to 5, with score 0 being awarded to no problem and score 5 being awarded to most severe problem.

Table 2: Reflux Finding Score

1. Subglottic edema [2 = present; 0 = absent]
2. Ventricular obliteration [2 = partial; 4 = complete]
3. Erythema/Hyperemia [2 = aretynoids only; 4 = diffuse]
4. Vocal fold edema [1 = mild; 2 = moderate; 3 = severe; 4 = polypoid]
5. Diffuse laryngeal edema [1 = mild; 2 = moderate; 3 = severe; 4 = obstructing]
6. Posterior commissure hypertrophy [1 = mild; 2 = moderate; 3 = severe; 4 = obstructing]
7. Granuloma/Granulation [2 = present; 0 = absent]
8. Thick endolaryngeal mucus [2 = present; 0 = absent]

The patients were followed up at 1 month and 3 months from initiation of medication & review scoring of RSI & RFS were done. Data was analyzed to ascertain the role of domperidone. The patients, who were under adequate treatment & following lifestyle modifications properly for at least 2 months but showing no improvement, were advised to follow a specially formulated reflux induction diet habit for 2 weeks & followed up to find out its impact.

Results: Out of total 108 cases, 20 cases were excluded from the study as they were below the cut-off margin for RFS score 9 (i.e. 7). Out of the remaining 88 cases, 60 (68.2%) were female and 28 (31.8%) were male. So female: male ratio was 2.14:1. Out of 60 female patients, 14 were below 30 years, 38 were within 30 to 50 years & 8 were above 50 years. Out of 28 male patients, 6 were below 30 years, 16 were below 30 years, 16 were within 30 to 50 years & 6 were above 50 years. The mean RSI score in each of these age groups for females were 17.6, 16.8 & 15.3 respectively & for males were 12.7, 15.8 & 11.7. Similarly the mean RFS for females were 11.3, 11.2 & 11.3 & for males were 10.3, 11.1 & 11 respectively.

Lumpy or sticky sensation in throat was the foremost presenting complain found in 56.8% of the study population. Soreness, pain & non-specific throat complaints were distant runner-up found in 20.5% of cases. Voice related problems were seen in 13.6% cases & chronic cough was found only in 6.8% cases.

Among the laryngeal signs of LPR, laryngeal edema including vocal cord edema, laryngeal erythema & posterior commissure hypertrophy were present in all the cases. Thick endolaryngeal mucus that is positive string sign was found in 47.7% cases. Subglottic edema and ventricular obliteration were rare findings, found only in 16% and 31.8% cases respectively. Granuloma was found in only 4.5% cases.
The study population was divided into 3 groups as per RSI score. The group A (RSI score <15), group B (RSI score 15-20) & group C (RSI >20) had respectively 38, 32 & 18 eseses. In these successive groups, the mean values of laryngeal erythema were found to be diminishing (3.7, 3.13 & 3.11). But the mean values of vocal fold edema (1.7, 1.8, 1.9), diffuse laryngeal edema (1.6, 1.8, 1.9) & posterior commissure hypertrophy (2.1, 2.2 & 2.4) were found to be rising with rising symptom scores. Both the group of patients (one group treated with pantoprazole-domperidone combination & the other with pantoprazole only) showed appreciable improvement in their mean RSI & RFS score at 1 month & 3 months follow-up. However, for the 1st group (pantoprazole-domperidone combination), the p-value was calculated to be <0.05. In the 2nd group, the p-value was >0.05 & was not statistically significant. Induction reflux diet, which we had advised to patients with persisting problems, was very effective in reducing RSI & RFS, p-value being <0.05.

**Discussion** : The term “laryngopharyngeal reflux” was coined by Dr. Jamie A. Koufman. Laryngopharyngeal reflux (LPR) is the backflow of stomach contents up the esophagus and into the throat. Lot of recent evidence has implicated reflux in development of chronic laryngeal and pharyngeal disorders. The harmful agents in the refluxate are primarily acid and activated pepsin. LPR is different from gastroesophageal reflux (GER). Mostly patients with GER, present to the gastroenterologist and typically have oesophagitis and heartburn. The patients of LPR, who have heartburn or oesophagitis, are very less (12%). The anatomic abnormality in LPR is believed to be at the upper oesophageal sphincter. Esophageal motility and acid clearance are usually normal. The refluxate in LPR spends very little time in the oesophagus and does most of the damage above the upper oesophageal sphincter. Significant upright daytime reflux is common in patients with LPR. In other words, LPR and GER appear to be somewhat different clinical variations of gastroesophageal reflux disease (GERD).

It has been estimated that 10 to 50% of patients with laryngeal complaints have a GER-related underlying cause. The symptoms those have been found to be associated with LPR are chronic or intermittent dysphonia, voice breaks, chronic throat clearing, excessive throat mucus, chronic cough, dysphagia, globus sensation, chronic or intermittent airway obstruction etc. Many laryngeal conditions have established correlation with LPR like reflux laryngitis, subglottic stenosis, carcinoma of larynx, contact ulcer and granuloma, posterior glottic stenosis, arytenoid cartilage fixation, paroxysmal laryngospasm, globus pharyngeus, vocal nodule, pachydermia laryngis, sudden infant death syndrome etc.

Currently different conditions like sinusitis, adenoid hypertrophy, dental caries, aphthous ulcer, Obstructive sleep apnea, otitis media, lung fibrosis, lung abscess etc are being linked to LPR.

The current gold-standard for diagnosing LPR is 24 hour ambulatory double-probe pH monitoring. One probe may be kept above the upper oesophageal sphincter and the other one about 5 cm above the lower oesophageal sphincter. The various types of electrodes available are unipolar glass electrodes, antimony electrodes and combined glass electrodes. They are inserted under local anaesthesia in outpatient setting. The electrodes can be put by endoscopy, fluoroscopy or under manometric control. Patient also carries a portable data logger tied with a waist belt. Data from the electrodes are recorded at 6-8 second intervals.

A recent study has demonstrated that detection of pepsin in throat sputum by immunoassay appears as a sensitive test to detect LPR. The pepsin immunoassay was 100% sensitive and 89% specific. But in our set-up these diagnostic tools are not readily available. LPR was used to be diagnosed clinically. We choose to use two simple diagnostic tools, REFUX SYMPTOM INDEX and REFUX FINDING SCORE. A RFS score greater than 7 has been used as a clinical diagnostic criteria.

From the results of our study, we see that LPRD is predominantly a disease in females. In both of the sexes, middle-aged persons are most often involved. The severity of disease in different age groups, as obtained from mean RFS score, seems to be similar in male & female. However, the symptom scores were much higher in females than males in respective age groups, except in middle age group. It seems that the females are more complaining in this regards, particularly in the extremes of ages.

Stickyness in throat was the foremost complaining feature & among the endoscopic signs laryngeal erythema, edema & posterior commissure hypertrophy were found in all the cases. Erythema diminishes with increasing severity of the disease & is not a reliable marker. But laryngeal edema & PCH were found to be a consistent marker of disease severity. Focal vocal fold edema & diffuse laryngeal edema appeared to be a similar marker of disease severity in moderate to severe group of disease. However, in mild disease focal vocal fold edema was a more consistent finding. Traditionally, reducing the stomach acid production &
lifestyle modifications to reduce the reflux episodes were the treatment for LPRD. There is debate regarding adding a prokinetic drug in the management of LPRD. The current study addresses this issue. In our study it was found that adding a prokinetic drug in the anti-reflux therapy gives statistically significant advantage.

It has also been recently explored that pepsin is the most damaging factor, rather than the acid. There is speculation that limiting the hydrogen ion intake reduces the acidity of the environment of laryngeal inlet that saves the laryngeal epithelium from damage. Thus an Induction reflux diet has specially been formulated, the idea is to limit intake of anything below pH 5. The role of this dietary habit is being evaluated in refractory cases of LPRD. In our study we found that this diet pattern is extremely helpful in reducing the symptoms & signs of refractory LPRD.

**Conclusion:** Since LPRD is a highly prevalent disease and is associated with different manifestations and disease process, it is critical to diagnose and treat LPR early. 24 hour ambulatory double probe pH metry is the investigation of choice. When ph-metry is not available, diagnosis can reliably be made by RSI and RFS score clinically.

Contrary to the earlier belief that laryngeal erythema is the most important sign of LPR, different studies are now revealing vocal fold edema to be more important. Our study also confirms that. We also found that severity of posterior commisure hypertrophy correlates well with the severity of the disease.

It was found in this study that adding prokinetic drugs to pantoprazole gives higher therapeutic benefit in the management of LPRD. Specially formulated induction reflux diet, that limits intake of anything below pH 5, is an appropriate supplement to the conventional anti-reflux therapy for refractory cases.

The other findings such as middle-aged female preponderance & more symptom score with respect to endoscopic findings score in females indicates that larger multicentric demographic studies are required in future that might reveal many sociological, psychological or behavioral aspects of LPR.

**References:**