Clinical Manifestations and Role of Proton Pump Inhibitors in the Management of Laryngopharyngeal Reflux

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Abstract Laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the throat that is into the hypopharynx. LPR is different from classical Gastroesophageal reflux disease (GERD) in many ways. Proton pump inhibitors have become the treatment of choice even though conflicting results exist in their response. Treatment requires acid suppression to be as complete as possible and treatment failure is not uncommon. In this article we present here our prospective study of 50 patients diagnosed as a case of LPR on the basis of reflux finding score and reflux symptom index. We tried to evaluate the role of PPI in LPR management by observing the effect of PPI on reflux finding score (RFS) and reflux symptom index (RFI) during the follow up period of 16 weeks.

Keywords Laryngopharyngeal reflux · GERD · Proton pump inhibitors

Introduction

The term reflux [derived from Latin word *re* (back) and *fluere* (to flow)] literally means backflow.

Laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the throat that is into the hypopharynx. There are numerous synonyms for LPR in the medical literature; reflux laryngitis, laryngeal reflux, gastropharyngeal reflux, pharyngoesophageal reflux, supraesophageal reflux, extraesophageal reflux, atypical reflux. The most accepted of these terms is extraesophageal reflux [1].

LPR is the term which was coined by James [2] and is accepted by the American Academy of Otolaryngology: Head and Neck surgery [1]. James [2] in a landmark article emphasized the otolaryngological 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 [2] and 1% [2] of patients to primary care physicians. Although there are no published figures as to the prevalence of LPR in general population James et al. [3] estimated that 50% of all patients presenting with voice or swallowing disorder exhibit LPR. LPR is one of the foremost recognised etiological factors behind the development of various inflammatory disorders of the upper aero-digestive tract.

Laryngopharyngeal reflux and Gastroesophageal reflux disease (GERD) are different disorders [2] LPR causes irritation and changes in the larynx. GERD is caused by the backflow of gastric contents into the esophagus, which leads to tissue damage or esophagitis and heartburn. It appears that the mechanism of LPR is different from those of GERD. LPR is not commonly post-prandial. Patients with LPR are predominantly upright (daytime) refluxers; there are no prolonged periods of acid exposure, no dysmotility and no prolonged esophageal acid clearance in LPR. As a result, in many patients with LPR, the amount and duration of esophageal reflux are in normal range.

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Although this level of esophageal reflux does not cause heart burn and esophagitis, the more fragile laryngeal epithelium may still be injured. The larynx and pharynx are also devoid of the acid clearance mechanism found in the oesophagus and thus is far more liable to peptic injury. For the esophagus, up to 50 reflux episodes [2] a day is considered normal. For the larynx, as few three episodes [2] a week has been shown to be associated with the development of significant disease. This increased sensitivity to damage may be an underlying cause of many diseases of airways; however the biological basis for this sensitivity to damage is not well understood. It is believed that the primary defect in GERD is lower esophageal dysfunction whereas the primary defect in LPR is upper esophageal sphincter dysfunction [1]. It is likely that these differences in mechanisms account for the differences in symptoms and manifestations of LPR and GERD. The vast majority of patients with LPR do not have esophagitis, the diagnostic *sin qua non* of GERD [2].

Patient with LPR present with nonspecific symptoms like globus sensation, vocal fatigue, hoarseness, chronic throat clearing, dysphagia, chronic cough [4]. They do not usually have symptoms of gastroesophageal reflux [2].

Laryngoscopic findings are also nonspecific. The most common laryngoscopic finding is reflux laryngitis [1]. The most frequently observed LPR related findings are interarytenoid erythema or hyperemia, infraglottic edema (pseudo sulcus), ventricular obliteration, posterior commissure hypertrophy and/or pachyderma, granuloma or granulation tissue formation, and thick excessive endolaryngeal mucus [5]. Pseudo sulcus vocalis, also known as infra-glottic oedema, is a pattern of oedema on the ventral surface of the vocal fold that extends from the anterior commissure to the posterior larynx. The presence of pseudo sulcus alone is suggestive of a diagnosis of LPR [6]. However there is often lack of correlation between symptoms and signs and as a result, laryngeal signs need not to be present in order to diagnose LPR [7]. A normal laryngeal examination cannot rule out the presence of LPR [8]. Observation of these findings along with the presence of suggestive laryngeal symptoms gives important information for the diagnosis.

Much effort has been spent in the past years on early detection of the problem with a simple, economical and non invasive instrument. Belfasky et al. developed simple non-invasive, economical instruments reflux symptom index and reflux finding score to help in the diagnosis of LPR.

Reflux finding score (RFS) [9] is an 8 item clinical severity rating scale based on fiberoptic findings. The scale includes most common laryngeal findings related to LPR, it has been concluded that any individual with RFS greater than 7 has more than 95% probability of having LPR.

These authors concluded that RFS accurately document treatment efficacy in patients with LPR. It demonstrates excellent inter and intraobserver reproducibility. RFS is easily administered, takes less than 1 min to complete, and manifests excellent inter- and intra-observer reproducibility. Although each item on RFS is entirely subjective, the overall finding score reliably documents improvement with antireflux therapy. It ranges from 0 to 26 (worst score). Reflux symptom index (RSI) [10] on the other hand is a 9 item self administered outcome instrument. It has been stated that it accurately documents symptoms of patients with LPR. This index appears to be valid and is highly reproducible. An RSI of more than 13 is considered to indicate LPR. It ranges from 0 to 45 (worst possible score).

We found patients where RFS was less than 7 but RSI greater than 13 but we excluded them from our study, this has been reported recently by Tamer [11].

Response to empiric treatment with PPI (the ‘Omeprazole test’) is a more common and acceptable initial diagnostic strategy for uncomplicated LPR [8]. Despite its weakness, dual probe pH monitoring remains the most specific and sensitive test available to diagnose LPR [7]. The establishment of diagnosis by pH monitoring for LPR is reserved by American Gastroenterological Association [7] for patients who do not respond to initial acid suppression and the use of pH monitoring as initial diagnostic study is also recommended in patients with more severe conditions possibly related to LPR such as sub-glottic stenosis and severe laryngospasm [8].

Standard therapeutic intervention for LPR includes life style modifications, medical and surgical treatment. Proton pump inhibitors have become the treatment of choice even though conflicting results exists in their response [7]. Unlike with GERD, response to PPI therapy in patients with LPR has been described as highly variable. Because of the lack of laryngopharyngeal protective mechanism, it is likely that only a small amount of acid reflux into the upper aero-digestive tract is capable of causing significant symptoms. For this reason treatment requires acid suppression to be complete, aggressive and prolonged therapy than GERD and treatment failure is not uncommon [8]. There are studies favouring PPI and favouring placebo treatment in the management of LPR [8].

PPI were introduced in 1980s. Proton pump inhibitors are the most potent suppressors of gastric acid secretion and they are inhibitors of gastric H⁺, K⁺ ATPase (proton pump). In typical doses these drugs diminish the daily production of acid (both basal and stimulated) by 80 to 95%. Of the PPIs, Five proton pump inhibitors are available for clinical use; omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole. These drugs have different substitutions on their pyridine and/or benzimidazole but are remarkably similar in their pharmacological

properties. Onset of action is fast with maximum acid inhibitory effect between 2 and 6 h after administration and duration of inhibition lasting up to 72–96 h. Since an acidic pH in the parietal cell acid canaliculi is required for drug activation and since food stimulates acid production, these drugs ideally should be given 30 min before meals. Since the proton pump inhibition is irreversible, acid secretion will be suppressed for 24–48 h or more until new pumps are synthesized [12]. Rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy. Omeprazole is a racemic mixture of R- and S-isomer, esomeprazole is the S-isomer of omeprazole as an improvement in its pharmacokinetic properties. Omeprazole has the highest risk for hepatic-based interactions, and rabeprazole and pantoprazole appear to have the lowest risk. Pantoprazole and lansoprazole are approved for intravenous administration. The most common side effects are nausea, abdominal pain, constipation, flatulence and diarrhoea. To the best of our reviewed knowledge no study exists in the indexed literature that has compared the efficiency of different proton pump inhibitors in the management of LPR.

Aim of Study

(i) To observe different signs and symptoms of LPR. (ii) To evaluate the role of PPI in the management of LPR by observing the effect of PPIs on RFS and RSI.

Materials and Methods

This prospective study was conducted in J.N. Medical college AMU Aligarh for a period of 2 years from July 2006 to July 2008. The materials for the present study were 50 patients of different age groups attending ENT OPD in JNMC AMU Aligarh having different symptoms of LPR. Patients were divided into different age groups. Reflux symptom index and reflux finding score were used to diagnose LPR.

The patients mainly belonged to the regions of various districts of western, northern and some parts of central Uttar Pradesh.

Inclusion Criteria

Patients of different age groups with symptoms of LPR for the last 1 month and with both reflux symptom index (RSI) >13 (Table 1) and reflux finding score (RFS) >7 (Table 2).

Table 1 Reflux symptom index

Complaint	Yes/ no	Duration
1. Hoarseness or problem with voice		
2. Frequent clearing of throat		
3. Excess throat mucus or postnasal drip		
4. Difficulty swallowing food, liquids or pills		
5. Coughing after having eaten or after lying down		
6. Breathing difficulties or choking episodes		
7. Troublesome or annoying cough		
8. Sensations of something sticking in throat or a lump in throat		
9. Heartburn, chest pain, indigestion or stomach acid coming up		

Each point is ranked from 0 (no problem) to 5 (severe problem). It ranges from 0 to 45 (worst possible score)

Table 2 Reflux finding score

1. Pseudosulcus	0 absent, 2 present
2. Ventricular obliteration	0 none, 2 partial, 4 complete
3. Erythema/hyperaemia	0 none, 2 arytenoid only, 4 diffuse
4. Vocal cord edema	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing (polypoidal)
5. Diffuse laryngeal edema	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing
6. Posterior commissure hypertrophy	0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing
7. Granuloma/granulation	0 present, 2 absent
8. Thick endolaryngeal mucus	0 absent, 2 present

It ranges from 0 (lowest possible) to 26 (highest possible)

Exclusion Criteria

Patients with some other obvious cause of symptoms and signs like infection, malignancy. Patient with history of antireflux medication in the preceding one month, patients with RFS less than 7 and/or RSI less than 13.

Procedure

Each patient underwent examination comprising of detailed history, physical examination to exclude other causes, indirect laryngoscopy, flexible laryngoscopy. The diagnosis of LPR on first visit was done on the basis of symptom scoring called reflux symptom index and laryngoscopic finding called reflux finding score.

Follow Up

Patients were followed for 16 weeks, on two occasions first at 8 weeks and then at 16 weeks. On each follow up visit patients symptoms were evaluated with reflux symptom index and laryngoscopic findings scored with reflux finding score.

Role of Proton Pump Inhibitor

Proton pumps like omeprazole 20 mg twice daily, esomeprazole 20 mg twice daily, rabeprazole 20 mg twice daily, pantoprazole 40 mg twice daily and lansoprazole 30 mg twice daily were used in the study. RFS and RSI was used to assess patients at first visit.

Effect of PPI on reflux finding score and reflux symptom index at each follow up visit was used to assess the role of PPI.

All data were coded and entered into SPSS 12. Any person with incomplete data was excluded from investigation. The paired sample *t*-test was used to evaluate the difference between reflux symptoms and findings at each treatment follow up.

Observations and Results

Total number of patients included in the study were 50, 30 (60%) cases were females, 20 (40%) were males. Male to female ratio in the study was 2:3. Age of the patients varied from 10 to 50 yrs. No patient was less than 10 yrs of age. Maximum numbers of patients were in the age group 31 to 40 yrs forming about 40% of the study group. Mean age of the study population was 38 years.

Table 3 Percent distribution of symptoms (RSI)

Symptoms	Total number of patients	Percentage
Hoarseness	18	36
Frequent clearing of throat	32, 2nd MC	64
Excess throat mucus	17	34
Difficulty in swallowing foods, liquids or pills	25	50
Cough after eating or after lying down	15	30
Breathing difficulties	15	30
Trouble some or annoying cough	28, 3rd MC	56
Foreign body sensation	37, 1st MC	74
Heartburn, chestpain, indigestion or stomach acid coming up	25	50

Table 4 Change of RSI with PPI therapy

Age group	Number of patients	Pre-treatment (RSI)	Post-treatment after 8 weeks	Post-treatment after 16 weeks
0–10	0	–	–	–
11–20	4	24	13	13
21–30	15	26	14	13
31–40	20	25	13	13
41–50	11	24	14	14
Total	50	24.75	13.5 ($P < 0.05$)	13.25

Fig. 1 Showing erythema over arytenoids

Foreign body sensation (Table 3) was the most common symptom present in 74% of patients followed by frequent clearing of throat in 64% and cough in 56% of patients.

Mean RSI of all patients was 24.75 before treatment with proton pump inhibitors. After 8 weeks of therapy with PPI mean RSI decreased to 13.5 and after 16 weeks of PPI therapy mean RSI dropped to 13.25 (Table 4). Significant change in RSI occurred after first 8 weeks of therapy in total and in all age groups and no further significant change occurred in the next 8 weeks.

Most common laryngeal finding was erythema/hyperemia (Fig. 1), followed by ventricular obliteration (Fig. 2) and posterior commissure hypertrophy (Table 5). Mean RFS of the patients was 12 before treatment with proton pump inhibitors. After 8 weeks of therapy with PPI mean RFS decreased to 9.5 and after 16 weeks of PPI therapy mean RFS dropped to 6.5 (Table 6) which was statistically significant. There was slight response after 8 weeks of therapy in physical findings in all age groups and significant response after 16 weeks of therapy in total and in all age groups.

Fig. 2 Showing ventricular obliteration

Table 5 Percentage distribution of signs (reflux finding score)

Findings	Number of patients	
Pseudo sulcus	25	50
Ventricular obliteration	38, 2nd MC	76
Erythema/hyperaemia	44, 1st MC	88
Vocal fold edema	26	52
Diffuse laryngeal edema	26	52
Posterior commissure hypertrophy	30, 3rd MC	60
Granulation/granuloma	20	40
Thickendolaryngeal mucus	15	40

Table 6 Change of RFS with PPI therapy

Age group	Number of patients	Pre-treatment (RFS)	Post-treatment RFS after 8 weeks	Post-treatment RFS after 16 weeks
0–10	0		–	–
11–20	4	12	10	6
21–30	15	13	9	7
31–40	20	11	9	6
41–50	11	12	10	7
Total	50	12	9.5	6.5 ($P < 0.05$)

Discussion

Laryngopharyngeal reflux has appeared in the otolaryngology literature since Delahunty et al. described vocal cord contact ulcer (vocal cord granuloma) in 1968 [13]

indeed, LPR, documented by pharyngeal pH monitoring was not reported until 1986. Before that time, many of these head and neck symptoms were presumed to result from vagally mediated reflexes, not from LPR. As early 1980s, many clinicians questioned whether backflow of gastric contents into the throat could account for laryngopharyngeal symptoms in the absence of heart burn, the primary symptom of GERD. Then Wiener et al. (1986) were the first to use concurrent oesophageal and pharyngeal pH monitoring (double probe) for diagnostic evaluation of patients with LPR symptoms and showed that there are separate episodes of reflux that go up to the laryngopharynx, which are distinct [14]. It was James [2] who first clearly differentiated between LPR and GERD. He implied that reflux in these patients was different than gastroenterology patients. In 1996 there was consensus conference report [15] on LPR with group of well known laryngologist and then in 2002 position statement on LPR was made and gave treatment recommendations [1].

Symptoms of LPR are protean; however the most common are hoarseness, globus pharyngeus, dysphagia, cough, chronic throat clearing, post nasal drip and sore throat. These symptoms are often intermittent or ‘chronic-intermittent’. However, these symptoms are not specific for LPR, and may be caused by rhinitis, asthma, laryngeal cancer, and many other pathologic conditions. Other manifestations in the head and neck that have been reported include asthma, sinusitis, and otitis media [1], obstructive sleep apnoea [16].

The most common manifestation of LPR is reflux laryngitis with or without granulation or granuloma formation [1]. In addition, reflux has been reported to be associated with subglottic stenosis, vocal nodules, reinkes edema, contact ulcer granuloma, laryngeal carcinoma, polypoid degeneration, laryngospasm, paradoxical vocal fold movement and vocal nodules [1]. The prevalence of symptoms attributed to LPR is in the range of 15–20%. The classical laryngeal physical findings of LPR reported in otolaryngology literature are edema and erythema the posterior commissure—so called posterior laryngitis. Recently, it has been suggested that there is an association between hypertrophy of Waldeyer’s ring (palatine tonsils, pharyngeal tonsils, lingual tonsil and intervening lymphoid tissue) lymphatics and LPR [17].

Diagnosis can be made on the basis of the symptoms and laryngeal findings but ambulatory pH monitoring remains the gold standard when diagnosis is in question. Other diagnostic tests like barium esophagography or esophagoscopy are far less sensitive for LPR. Bilgen et al. 2003 concluded that empiric trial of PPI is an alternate for the 24 h double probe pH monitoring for the diagnosis of LPR [18].

Maximum numbers of patients in our study were in the age group 31–40 yrs forming about 40% of the study

group. Females (60%) outnumbered the males (40%) in the current study. This result is in accordance with the indexed literature where females outnumbered the males like that of Belfasky and Postma [9], Issing and Karkos [19], Bilgen and Ogut [18], Mesallam and Stemple [11], Toros and Toros [20]. Criteria for diagnosis in these studies were pH monitoring except for Bilgen, Mesallam and Toros. Where it was RFS, RSI, modified reflux symptom index (MRSI).

Most common symptom in the study was found to be Globus sensation in 74% of patients followed by frequent clearing of throat in 64% of patients and troublesome or annoying cough in 56% of study population. Least common symptom was breathing difficulties. Other studies have also found globus pharyngeus as most common symptom like studies of Mesallam and Stemple [11], Karkos and Yates [21], Issing and Karkos [19], while some studies have found other most common symptoms of LPR like throat burning (Pieter Noordzij and Khidir) [22], Hoarseness in 71% (Koufman [2]), cough (Eubanks et al. [23]), frequent clearing of throat (Toros and Toros [20]).

Most common laryngoscopic sign in the study was found to be erythema/hyperaemia in 88% of patients followed by ventricular obliteration in 76% of patients and posterior commissure hypertrophy in 60% of study population. Other studies have also found erythema as most common sign like studies Book and Rhee [24], Mesallam and Stemple [11], Karkos and Yates [21] and Toros and Toros [20].

In contrast to our study other authors have noted other most common laryngoscopic signs like posterior commissure hypertrophy by Belfasky and Postma [9], Partial ventricular obliteration by Tezer and Kockar [25]. We noted Pseudo sulcus in only 50% of our study group whereas Belfasky et al. [6] in a study of 30 patients diagnosed on the basis of pH monitoring found pseudo sulcus in 70% of study subjects and concluded that sensitivity and specificity of pseudo sulcus in the diagnosis of LPR are 70 and 77% respectively.

We used RSI and RFS to assess the role of PPI. We found significant improvement in both symptoms and signs after 4 months of PPI therapy. Symptomatic improvement was obvious after 2 months of therapy but laryngeal signs took 4 months to show improvement.

Our study showed similar results to other studies done for response of RFS to PPI like studies of Belfasky and Postma [9], Bilgen and Ogut [18]. Our study lacked pH monitoring and these two studies employed the same.

Overall physical finding did not change significantly after 8 weeks of therapy but it changed so after 16 weeks of therapy and this is in accordance with the literature. Similar results were obtained in other studies like study by Belfasky and Postma [9] Belfasky et al. [10]. The difference in their study as compared to our study is that we

diagnosed LPR on the basis of RSI and RFS and they diagnosed it on the basis of pH monitoring.

There is currently no accepted protocol for the most effective treatment of patients suspected of having LPR. Among the unresolved issues are the dosing and length of therapy with PPIs and the role of H2RAs in those unresponsive to PPIs alone. Although we did not use H2RAs in our study but the fact is studies using H2RAs have produced only mild to moderate improvements at best as reported by Koufman [2], Vaezi et al. [5]. First study to use PPI was by Kamel [26] who used omeprazole. Recent studies have used the more effective acid-suppressive agents, PPIs. However, due to lack of consensus, most studies employed PPIs at varying doses and different duration of treatment. The PPIs are commonly given before meals in most of the studies. Twice-daily dosing is usually employed to better control both nocturnal and daytime esophageal acid exposure.

We did not encounter any resistant patient to PPI as resistance is reported to be seen in significant number of patients as reported by Amin [27]. We used omeprazole 20 mg twice daily, esomeprazole 20 mg twice daily, rabeprazole 20 mg twice daily as compared to higher doses used in other studies. Our study after PPI therapy found dramatic response in signs and symptoms and showed unexpectedly 100% response rate with PPI therapy, even though there are different response rates reported in literature.

Overall we observed in patients that twice daily proton pump inhibitor for treatment of laryngopharyngeal reflux resulted in good response rate and treatment must be continued for at least 4 months. Laryngeal signs may take more time to resolve as also reported in literature.

Treatment of LPR of more than 6 months may be indicated to attain full resolution of physical findings and to reduce the risk of return of symptoms.

Termination of treatment based on the presumption that LPR symptoms are getting better alone may be pre-mature. This conclusion concurs with the view of consensus conference report 1997 on LPR that suggested twice daily PPI treatment to be continued for a minimum of 6 months.

Our study is in accordance with many studies reported in literature like studies by Jaspersen and Weber [28] who demonstrated complete (100%) symptom free healing of LPR after a 4 weeks treatment with 40 mg omeprazole per day as also demonstrated in our study; Kamel and Hanson [26] found a 92% response rate; Wo and Hunter [29]; Hanson et al. [30]; Metz and Childs [31] in a study of 10 patients of reflux laryngitis who were treated by PPI (20 mg omeprazole) for 1 month found a symptomatic improvement in 60%; Shaw and Searl [32] in a study of 68 patients of reflux laryngitis who were treated with omeprazole 40 mg for 3 months showed symptomatic

improvement in 60% with the exception of granuloma formation; Pieter Noordzij and Khidir [22]; Tauber and Gross [33] and Williams and Szczesniak [34] reported 47 and 63% response rates at 6 and 12 weeks, respectively, with omeprazole; Delgaudio [8]; Issing and Karkos [19]; Bilgem and Ogut [18]; Toros and Toros [20].

Our study is in contrast to other studies which illustrate the relative lack of acid suppressive therapeutic success in treating patients with suspected LPR like studies by Vaezi et al. [5]; Iuga and Ehrer [35]; Wo and Koopman [36]; Steward et al. [37]; Karkos and Wilson et al. [21].

Over-diagnosis of LPR may be the reason for the variable response rate reported in uncontrolled trials, and the confusion in the results of placebo-controlled studies. In this scenario of controversy stills the recommendation of twice daily dosing of PPI by American academy of otolaryngologists holds true as also demonstrated in our study.

Conclusion

To conclude in nutshell, although LPR is a common condition presenting in ENT settings, the symptoms and signs may be complex. Most clinicians rely on their clinical judgement for diagnosing this condition. The limitations of patient symptoms and pH testing in diagnosing LPR have motivated other investigators to quantify laryngeal findings attributed to reflux. The reflux finding score and reflux symptom index of Wake Forest University are valuable tools for diagnosing LPR as used in our study. RFS of more than 7 and RSI of more than 13 are associated with high likelihood of LPR. Our patients of LPR responded within 2 months of therapy, though laryngeal signs took more time to resolve, about 4 months. In most patients with LPR, twice daily PPI is needed and it should be prescribed for not less than 4 months. Our results are in accordance with the recommendations of consensus conference report (1997) and American academy of otolaryngology and head and neck surgery (2002). Even though we did not find any patient who did not respond, but as reported in literature treatment failures are not uncommon. There are many studies which do not favour PPI over placebo, so we need to perform more well designed, prospective large scale, probably multi-centeric studies to find the role of PPI in LPR.

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