Research Article

Treating laryngopharyngeal reflux with proton-pump inhibitors - An observational study

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ABSTRACT

Background: 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. Majority of such patients present with globus pharyngeus, cough, foreign body sensation in throat, and hoarseness. **Objectives:** Conflicting results appear in literature for the role of proton-pump inhibitors (PPIs) in LPR. Our aim in this study is to evaluate the role of PPI based on their effect on reflux finding score (RFS) and reflux symptom index (RSI). **Materials and Methods:** This prospective observational study was conducted in the Department of ENT and HNS of Government Medical College, Srinagar, for 3 years from 2015 to 2018. The materials for the present study were 70 patients of different age groups attending the ENT Outpatient Department (OPD) having different symptoms of LPR diagnosed on the basis of RFS >7 and RSI >13. Of them, 20 lost to follow up, and finally, 50 patients were followed as per the protocol. Patients were divided into different age groups. **Results:** A total number of patients included in the study were 50; 35 (70%) cases were females and 15 (30%) were males. A maximum number of patients were in the age group 31–40 years forming about 40% of the study group. Mean RSI of all patients was 24.4 before treatment with PPIs. Significant change in RSI occurred after the first 8 weeks of therapy, and no further significant change occurred in the next 16 weeks. Mean RFS of the patients was 13.2 before treatment with PPIs. There was a slight response after 8 weeks of therapy in physical findings and significant response after 16 weeks of therapy. **Conclusion:** PPIs are treatment of choice in patients with LPR and treatment should be continued for at least 4 months.

KEY WORDS: Laryngopharyngeal Reflux; Gastroesophageal Reflux Disease; Reflux Finding Score; Reflux Symptom Index; Proton-Pump Inhibitors; Treatment, Response

INTRODUCTION

Laryngopharyngeal reflux (LPR) was coined by James[1] in the year 1991 and is described as the backflow of gastric contents into the laryngopharynx, whereby acid comes in contact with laryngopharyngeal pharynx leading to its irritation.[2]

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LPR has been given various names in literature such as supraesophageal reflux, extraesophageal reflux, reflux laryngitis, laryngeal reflux, gastropharyngeal reflux, and pharyngoesophageal and atypical reflux.[2]

Review of literature reveals that approximately 10% and 50% of patients attending outpatient section of the ENT department and voice centers, respectively, are affected by this condition.[1,2]

Gastroenterologists and otolaryngologists have a different perspective of this condition. On the one hand, gastroenterologist believe that LPR is just a manifestationof gastroesophageal reflux disease (GERD), while on the other

hand, otolaryngologists believe that LPR and GERD are completely different in mechanisms and clinical manifestations.

An attempt to clear this confusion was done by James[1] in 1991 who highlighted the difference between the two entities. James[1] explained that the mechanisms for LPR are vagal afferent stimulation by acid and the direct laryngeal contact of laryngopharynx with acid.

Typical symptoms of GERD such as heartburn and esophagitis do not bother these patients and are seen in about 6–43% of such patients, which is quite low as compared to patients of GERD.[3]

LPR usually presents as throat clearing, globus sensation, hoarseness, sore throat, odynophagia, cough, and excessive phlegm. The classical findings are laryngeal edema/erythema, ventricular obliteration, thick endolaryngeal mucus, pseudosulcus, posterior commissure hypertrophy, pharyngeal wall edema and erythema, tongue and tonsil hypertrophy, and erythema of the anterior tonsillar pillar.[4]

The pH-impedance monitoring which was until now the gold standard for the diagnosis of LPR is losing its credibility because pH-impedance monitoring has many flaws such as the high-cost procedure and high rates of false positive and false negative.[4]

Response to the empirical therapy of twice daily, proton-pump inhibitor (PPI) for 1 month is a cost-effective diagnosis method for LPRD.[4]

Various scoring methods and instruments have been devised for the diagnosis and monitoring of response to therapy. Instrument used in literature are Reflux Finding Score (RFS); LRG; Chronic Posterior Laryngitis index; Vaezi Index; LPR index (LRDI); Laryngoscopic grading scale; Reflux symptom index (RSI).[4]

RFS is the most common followed by RSI and Vaezi *et al*. instrument. RSI and RFS have been widely used for diagnosis of LPR as they are simple, inexpensive, and non-invasive.

RSI and RFS were developed by Belafsky *et al*.[5,6]

RSI[5] is self-administered outcome instrument and consists of 9 items. An RSI of >13 is considered to indicate LPR. It ranges from 0 to 45.

RFS[6] is a clinical severity rating scale-based laryngoscopic findings. It consists of 8 items. Patients with RFS >7 have more than 95% probability of having LPR. It ranges from 0 to 26.

Treatment for LPR includes lifestyle modifications and medical and surgical treatment. The most common class of drugs prescribed for LPR is the PPI.

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 PPI has to be prescribed twice a day for a period of about 3–6 months.[7]

There are six PPIs approved by the United States Food and Drug Administration (FDA). Omeprazole was the first clinically useful PPI which came into market. The other PPIs introduced later on include rabeprazole, lansoprazole, pantoprazole, esomeprazole, and dexlansoprazole.[8]

PPIs are membrane permeable, acid-labile weak bases. These drugs have high chances of premature activation and degradation by luminal gastric acid, and to prevent such degradation, these drugs are packaged in a variety of delivery systems. These systems include enteric coated tablets and gelatin capsules.[8] PPIs are absorbed in the proximal small bowel.

The serum half-life of single release PPIs is extremely short (1–2 h). Newer PPI tenatoprazole is in clinical trials, not yet approved by thae FDA, and has a serum half-life of 7 h.[8]

The most common side effects are nausea, abdominal pain, constipation, flatulence, and diarrhea. Long-term use can cause chronic interstitial nephritis leading to chronic kidney disease and end-stage renal disease.

PPIs have been shown to benefit patients with LPR in many studies[9] while some studies/trials showed its insignificance in treatment in view of over diagnosis of LPR, no perfect gold standard diagnostic modility, and interobserver variability in administering LPR instruments.

Authors evaluated the role of PPI in the management of LPR by observing the effect of PPIs on RFS and RSI which are most commonly used instruments in literature.

Ethical clearance was not required as this was purely a prospective observational study where no new drug was given or any new intervention done.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of ENT and Head and Neck surgery of Government Medical College, Srinagar, for 3 years from July 2015 to July 2018.

A total of 70 patients with different symptoms of LPR attending OPD were initially taken in this study. Of them, 20 lost to follow up, and finally, 50 patients were followed as per the protocol. RSI and RFS were used to diagnose LPR.

Only those patients who had LPR symptoms for 1 month and whose RSI [Table 1] and RFS [Table 2] were >13 and 7, respectively, were enrolled in the study after taking proper consent.

Patients with any other obvious cause for such symptoms such as malignancy and history of anti-reflux therapy in the past 1 month were excluded freom the study.

History and examination of each suspected patient were done. Flexible fiberoptic laryngoscopy was performed in all cases. Only those cases who fulfilled the selection criteria were included in the study.

RFS and RSI scores of each selected patient were noted at the first visit.

Each patient was put on twice a day PPI therapy. PPI used in the study was pantoprazole 40 mg daily, lansoprazole 30, omeprazole 20 mg, esomeprazole 20 mg, and rabeprazole 20 mg.

Each patient was followed for 16 weeks. Fiberoptic laryngoscopic examination was done on two occasions: First at 8 weeks and then at 16 weeks.

On each of these visits, RFS and RSI were administered. Effect of PPI (as tabulated) on RFS and RSI at each follow-up visit was used to assess the role of PPI. The paired sample *t*-test was used to evaluate the difference between reflux symptoms and findings at each treatment follow-up.

RESULTS

A total number of patients included in the study were 50; 35 (70%) cases were females and 15 (30%) were males.

Age of the patients varied from 10 to 50 years. A maximum number of patients were in the age group of 31–40 years forming about 40% of the study group. Mean age of the study population was 30 years.

Mean RSI of all patients was 24.4 before treatment with PPIs. After 8 weeks of therapy with PPI, mean RSI and individual RSI of different age groups decreased to 13 which was statistically significant, and after 16 weeks of PPI therapy, mean/individual age group RSI dropped to 12.6 and the drop was not significant [Table 3].

Mean RFS of the patients was 13.2 before treatment with PPIs. After 8 weeks of therapy with PPI, mean/individual age group RFS decreased to 12 which was insignificant, and after 16 weeks of PPI therapy, mean/individual age group RFS dropped to 6.2 [Table 4] which was statistically significant.

We observed from the drop in RFS that significant improvement in laryngoscopic signs takes about 16 weeks, while from drop in RSI, we observed that significant improvement in symptoms occurs early after 2 months of therapy.

DISCUSSION

PPI therapy for LPR treatment has been criticized because PPI therapy is based on a poor level of evidence.[7]

The purpose of our study was to report our experience of the role of PPIs in the treatment of LPR by observing the effect of PPI on RFS and RSI.

The age group of 31–40 years was most commonly involved forming about 40% of the study group. Females (60%) were seen to be affected more than males (40%) in the current study. Female predominance was also seen in the studies of Issing, *et al*.[10] Bilgen, *et al*.[11] Mesallam, *et al*.[12] Toros, *et al*.[13] and Belafsky.[5]

Symptomatic improvement was obvious and RSI decreased significantly after 2 months of therapy. Laryngeal signs took 4 months to show improvement and RFS decreased significantly only after 4 months of therapy.

Table 1: RSI

Symptoms	Yes/no	Duration	Score
1. Hoarseness			
2. Frequent clearing of the throat			
3. Excess throat mucus			
4. Difficulty in swallowing foods, liquids, or pills			
5. Cough after eating or after lying down			
6. Breathing difficulties			
7. Troublesome or annoying cough			
8. Foreign body sensation			
9. Heartburn, chest pain, indigestion, or stomach acid coming up			

Each symptom is ranged from 0 (No problem) to 5 (Severe problem). The total score ranges from 0 (lowest possible) to 45 (highest possible), RSI: Reflux symptom index

Studies done for the response of RFS to PPI such as the studies of Belafsky *et al*.[5] and Bilgen *et al*.[11] showed similar results but contrary to our study; these studies used pH monitoring for diagnosis. Patigaroo *et al*.[14] in a similar study done in demographically different subset of patients but with similar selection criteria found similar results.

Table 2: RFS

1. Pseudosulcus (subglottic edema)	0 - absent 2 - present
2.Ventricular obliteration	0 - none 2 - partial 4 - complete
3. Erythema/hyperemia	0 - none 2 - arytenoids 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 to 26 (worst score), RFS: Reflux finding score

In contrast to our findings, Lam *et al*.[15] reported that only 29% of patients showed significant improvement in RSI after 4 weeks and 12 weeks of treatment were required to reach 75%improvement. Park *et al*.[16] found 72% response rate after 4 months of treatment.

We did not use H2 receptor antagonists (H2RAs) in our study, but the fact is studies using H2RAs have produced only mild to moderate improvements at best as reported Koufman[1] and Vaezi *et al*.[17]

Kamel *et al*.[3] were the first one to use PPI (omeprazole) for LPR, and since then, many studies have been done to find the role of PPI in LPR.

Most of the studies used twice-daily dosing to achieve better control of nocturnal and daytime esophageal acid exposure.

Resistance to PPI is reported to be seen in a significant number of patients as reported by Amin *et al*.[18] who, in their study, noted that 44% of LPR patients have resistance. We found no such resistance in our patients.

We used omeprazole 20 mg twice daily, esomeprazole 20 mg twice daily, and rabeprazole 20 mg twice daily as compared to higher doses used in other studies. Response rate to PPI in our study was 100%, while there are different response rates reported in literature.

Table 3: Change of RSI with PPI therapy

Age group (years)	Number of patients	Pre-treatment RSI	Post-treatment after 8 weeks	Post-treatment after 16 weeks
0–10	0	0	0	0
11–20	4	24	13	12
21–30	14	25	13	13
31–40	20	26	14	13
41–50	9	24	13	13
51–60	3	23	12	12
	Total (50)	Mean RSI (24.4)	Mean RSI (13)	Mean RSI (12.6)

RSI: Reflux symptom index, PPI: Proton-pump inhibitors

Table 4: Change of RFS with PPI therapy

Age group (years)	Number of patients	Pre-treatment RFS	Post-treatment after 8 weeks	Post-treatment after 16 weeks
0–10	0	0	0	0
11–20	4	12	11	6
21–30	14	13	12	6
31–40	20	14	13	7
41–50	9	13	11	5
51–60	3	14	13	7
	Total (50)	Mean RFS (13.2)	Mean RFS (12)	Mean RFS (6.2)

RFS: Reflux finding score, PPI: Proton-pump inhibitors

PPI in twice-daily doses for the treatment of LPR resulted in good response rate as seen in our study. Treatment must be continued for at least 4 months as laryngeal signs may take more time to resolve as also reported in literature.

As patients become symptom free within 2 months, but treatment should not be terminated prematurely before at least 4 months. Consensus Conference Report 1997 on LPR viewed similarly and suggested that twice-daily PPI treatment is to be continued for a minimum of 6 months.

Many studies/trials have supported the effectiveness of PPIs in treating LPR-related symptoms. Guo *et al*.[7] in 2016 in largest meta-analysis of 14 eligible randomized controlled trials found that PPI therapy could improve reflux symptoms significantly compared with placebo in patients with LPR. Lam *et al*.[15] in a trial similarly demonstrated that PPI therapy improved reflux symptoms significantly compared with placebo. Besides this meta-analysis and trial, double dose PPI for LPR has been favored by many studies reported in literature such as studies by Kamel *et al*.[3] who found a 92% response rate; Jaspersen *et al*.[19] demonstrated 100% response; Wo *et al*.[20], Hanson, *et al*.[21] and Metz *et al*.[22] found 60% response rate; Shaw *et al*.[23] in a study of 68 patients of reflux laryngitis found 60% response rate; and Noordzij, *et al*.[24], Tauber *et al*.[25] and Williams *et al*.[26] reported 47 and 63% response rates at 6 and 12 weeks, respectively.

Our study is in contrast to other studies which illustrate the lack of role of PPI in treating patients with suspected LPR such as studies by Vaezi, *et al*.[17] Eherer, *et al*.[27] Wo, *et al*.[28] Steward, *et al*.[29] and Karkos *et al*.[30]

Similarly Liu *et al*.[31] and Qadeer *et al*.[32] in 2006 in their meta-analysis suggested that PPIs and placebo therapy are similarly effective in improving LPR symptoms in adult patients. Reichel *et al*.[33] in a double-blinded, randomized controlled trial showed no significant difference between PPI and placebo in improving RSI and RFS.

The main limitation of this study is that we did not use pH monitoring/pH impedance in our patients to confirm reflux instead used RFS and RSI. We relied completely on the observation of Belafsky *et al*. that the probability of LPR is >95% if RFS is >7.

In this scenario of controversy, twice-daily dosing of PPI should be prescribed for not <4 months as demonstrated in our study and as advised by the American Academy of Otolaryngologists.

CONCLUSION

ENT surgeons commonly see patients with signs and symptoms of LPR. Treatment is practically started on the basis of signs and symptoms, and pH monitoring is not commonly done for diagnosis.

The RFS and RSI developed by Belafsky *et al*. are valuable tools for diagnosing LPR and for monitoring the treatment. Twice-daily PPI is needed for patients of LPR and it should be prescribed for not <4 months because laryngeal signs do not disappear completely before 4 months of therapy and it is premature to terminate the treatment before 4 months.

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