Effect Of Prokinetic Drug And Proton Pump Inhibitor On Laryngopharyngeal Reflux

Dr. Navin Agrawal[1], Dr. Vishal Hansrajani[2], Dr. Chhavi Agrawal[3], Dr. Sonakshi Kapoor[4*], Dr. Shivam Narang[5], Dr. Urvashi Singh[6], Dr. Raksha Wadhwani[7]

DOI Number: 10.4704/nq.2022.20.14.NQ88001 **Neuro Quantology 2022; 20(14):01-06**

INTRODUCTION

Laryngopharyngeal reflux (LPR) is defined as the retrograde movement of gastric contents into the larynx, pharynx and upper aerodigestive tract. LPR is caused by retrograde flow of stomach contents via the oesophagus into the larynx. It shares a similar pathophysiology to gastroesophageal reflux disease (GERD). LPR is a distinct entity, which can exist in patients with or without symptoms of GERD. (1)

The most common symptoms of LPR are excessive throat clearing, coughing, difficulty in swallowing, hoarseness, dysphonia and globus pharyngeus (Sensation of lump in the throat). Hoarseness is generally a fluctuating symptom that occurs in the morning and improves during the day. Laryngopharyngeal symptoms are increasingly recognized by general physicians, lung specialists and ear, nose and throat (ENT) surgeons. (2)

Diagnosis can be made through a combination of medical history, physical examination and one or more tests. Tests may include: An endoscopic examination, an office procedure that involves viewing the throat and vocal cords with a flexible or rigid viewing instrument, pH monitoring, which involves placing a small catheter through the nose and into the throat and oesophagus; here, sensors detect acid, and a small computer worn at the waist records findings during a 24-hour period. Newer pH probes placed in the back of your throat capsules placed higher up in the oesophagus may be used to better identify reflux.

Treatment of LPR consists of dietary changes and changes in habits such as weight loss, quit smoking, avoiding alcohol, and not eating immediately before bedtime. Dietary restrictions include caffeine, chocolate, aerated beverages, fat, tomato sauce, and red wine. These modifications have been shown to be a significant independent determinant of the response to medicamentous treatment. (3)

Current treatment recommendations include lifestyle changes and antacid medications such as histamine-2 receptor antagonists (H2 antagonists) and proton pump inhibitors (PPIs), which suppress acid production by directly acting on the H^+K^+ATPase of parietal cells. (4)

Prokinetic agents are medications that help to control acid reflux, restores gastric motility with increasing of Lower Oesophageal Sphincter Tone, cause the contents of the stomach to empty faster and oesophageal motility has been developed and used frequently in the treatment of GERD. (5)

The present study is to characterise the clinical modes of presentation and the effects of antacid and prokinetics in the management of LPR.

***Corresponding Author:** Dr. Sonakshi Kapoor
Address: [1]Professor & HOD, Department of ENT, Index Medical College Hospital & Research Center, Indore (MP)
[2.3]Associate Professor, Department of ENT, Index Medical College Hospital & Research Center, Indore (MP)
*[4,5,6,7] Pg Resident 3, Department of ENT, Index Medical College Hospital & Research Center, Indore (MP)
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest
Received: **Accepted:**

AIM:

To characterise the clinical modes of presentation and the effect of Antacid and Prokinetics in the management of reflux.

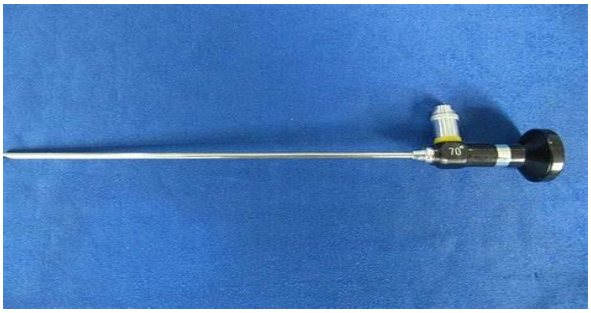
MATERIALS & METHODS

The present study was a hospital based, observational study involving 100 patients of Laryngopharyngeal Reflux diagnosed on the basis of patient complaints (Reflux Symptom Index) This study was conducted for a duration of 18 months, in the Otorhinolaryngology OPD of Index Medical College and Research Centre, Indore.

Methodology

1. We evaluated 100 patients in ENT OPD of Index Medical College, Hospital & Research Centre who were selected after getting their informed consent and were subjected for complete oral cavity, oropharyngeal, and laryngeal examination with video laryngoscopy 70 degrees and 90 degrees with non-invasive technique under topical anaesthesia.

a) Endoscopic Unit



b) 70 degree rigid endoscope

2. Patients above the age of 18years were included and were assigned to each of the three groups alternatively

a. Patients on proton pump inhibitors alone
b. Patients on prokinetics alone
c. Patients on combination of proton pump inhibitors and prokinetics.

3. The patients were subsequently followed up at

a. 10 days b. 4 weeks c. 8 weeks d. 12 weeks

1). REFLUX SYMPTOM INDEX-

Within the last MONTH, how did the following problems affect you? 0- no problem, 5-severe problem (Source: Belafsky et al)

S.NO	SYMPTOMS	SCORE
1.	Hoarseness or a problem with your voice	0 1 2 3 4 5
2.	Clearing your throat	0 1 2 3 4 5
3.	Excess throat mucus or postnasal drip	0 1 2 3 4 5
4.	Difficulty swallowing food, liquids or pills	0 1 2 3 4 5
5.	Coughing after you ate or after lying down	0 1 2 3 4 5
6.	Breathing difficulties or choking episodes	0 1 2 3 4 5
7.	Troublesome or annoying cough	0 1 2 3 4 5
8.	Sensations of something sticking in your throat or lump in your throat	0 1 2 3 4 5
9.	Heartburn, chest pain, indigestion or stomach acid coming up	0 1 2 3 4 5

2) REFLUX FINDING SCORE-

Clinical examination of patients was done under following headings as **Reflux Finding Score** (developed by Belafsky) **RFS 7 or more is suggestive of LPR.**

1. Subglottic oedema
2. Ventricular obliteration
3. Erythema
4. Vocal fold oedema
5. Diffuse Laryngeal oedema
6. Posterior commissure hypertrophy
7. Granuloma/granulation tissue
8. Thick endo-laryngeal mucus

Reflux Finding Score (RFS).

Subglottic edema	0 – absent / 2 – present			
Ventricular obliteration	Partial – 2 points		Complete – 4 points	
Erythema/hyperemia	Arytenoids only – 2		Diffuse – 4	
Vocal fold edema	Mild – 1	Moderate – 2	Severe – 3	Polypoid – 4
Diffuse laryngeal edema	Mild – 1	Moderate – 2	Severe – 3	Obstructive – 4
Posterior commissure hypertrophy	Mild – 1	Moderate – 2	Severe – 3	Obstructive – 4
Granuloma /granulation tissue	Absent – 0 / Present – 2			
Thick endolaryngeal mucus	Absent – 0 / Present – 2			

RESULTS:

Table 1: Pearson Correlation between reflux finding score and reflux symptom index

		Reflux symptom index
Reflux finding score	Pearson Correlation	-0.056
	Sig. (2-tailed)	0.579
	N	100

Table shows the Pearson Correlation between reflux finding score and reflux symptom index.

It was found that reflux finding score has a negative correlation with the reflux symptom index with Pearson Correlation co-efficient of -0.056. That means reflux finding score increases, reflux symptom index decreases. However, the p value of this correlation was insignificant with p value of 0.579.

Table 2: Comparing Reflux finding score in follow ups

Reflux finding score	Baseline	1st follow up	2nd follow up	3rd follow up	4th follow up
0	0	0	1	17	58
1	0	0	1	2	1
2	0		10	29	14
3	0	1	11	11	3
4	0	5	16	9	6
5	0	12	14	8	2
6	0	17	17	9	3
7	7	19	5	3	2
8	18	16	13	4	3
9	13	8	5	5	5
10	28	9	6	3	3
11	11	3	1	0	0
12	9	7	0	0	0
13	6	3	0	0	0
14	5	0	0	0	0
15	3	0	0	0	0

Table 2. shows the comparison in reflux finding score in follow ups. It was found that reflux finding score was improved from 10 score (majority had this score; n=28) to 7 (n=19)at first follow up to 6 (n=17) at second follow up, 2 (n=29) at third follow up and 0 (n=58) at the end of 4th follow up.

Table 3: Comparing reflux symptoms score in follow ups

Reflux finding score	Baseline	1st follow up	2nd follow up	3rd follow up	4th follow up
0	0	0	15	44	70
1	0	0	1	1	3
2	0	2	8	7	3
3	0	1	3	4	0
4	0	8	10	10	8
5	0	8	16	9	5
6	0	6	8	4	0
7	0	4	11	4	3
8	0	12	8	8	3
9	0	3	5	3	2
10	0	18	7	1	0
11	0	11	3	2	1
12	0	4	0	0	0
13	12	5	3	1	0
14	6	0	0	0	0
15	43	11	0	0	0
16	0	0	0	0	0
17	5	1	0	0	0
18	8	4	2	2	2
19	1	0	0	0	0
20	22	2	0	0	0
21	0	0	0	0	0
22	0	0	0	0	0
23	2	0	0	0	0
24	1	0	0	0	0

Table 18 shows the reflux symptoms score in follow ups. It was found that reflux symptoms score was improved from 15 score (majority had this score; n=43) to 10 (n=18) at first follow up to 5 (n=16) at second follow up, 0 (n=44) at third follow up and 0 (n=70) at the end of 4th follow up.

DISCUSSION:

Laryngopharyngeal reflux disease (LPRD) refers to an inflammatory reaction of the mucous membrane of pharynx, larynx and other associated respiratory organs, caused by a reflux of stomach contents into the esophagus.(6)

In present study we tried to characterized the clinical modes of presentation and the role of Antacid and Prokinetics in the management of reflux. For the purpose of comparison we divided the study cohort based on the proton pump inhibitor and prokinetic drug used in the management of laryngopharyngeal reflux. There were 34 patients who were on Proton pump inhibitor alone, 33 were on Prokinetic alone and 33 patients were on the combination of Prokinetic+ Proton pump inhibitor.

Belafsky, an American physician, has systematised 9 most common occurrences in the form of Reflux Symptom Index (RSI). Based on the number of this index a physician can either confirm or rule out existence of LPR. (Score of 13 or higher). (7) In the present study we used the same principle. Previous study has also shown that the RSI value was significantly higher in untreated LPR patients than in controls (p<0.001). The authors concluded that the questionnaire shows high reproducibility and validity because the accuracy in documenting symptom improvement of patients with LPR. (8) One challenge in diagnosing LPR is that the symptoms of the LPR with LPR disease lack sufficient specificity to confirm LPR and thus to rule out other causative agents. In fact, several studies have shown a poor correlation between LPR symptoms, laryngeal findings, and findings from hypopharyngeal pH registrations. (9,10) In agreement to this in present study it was found that reflux finding score has a very poor negative correlation with the reflux symptom index with Pearson Correlation co-efficient of -0.056. That means reflux finding score increases, reflux symptom index decreases, but poorly correlated and insignificant.

In an attempt to identify the most specific laryngoscopic signs of LPR, Belafsky et al developed the Reflux Finding Score (RFS) based on the findings of fibreoptic laryngoscopy.(1) This scale evaluates eight items that comprise the most common laryngoscopic findings in patients with LPR: subglottic edema; ventricular

obliteration; erythema or hyperemia; vocal fold edema; generalized laryngeal edema; posterior commissure hypertrophy; granuloma or granulation tissue; and excess mucus in the larynx. 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. In that study, this scale showed excellent reproducibility and, although each item alone was unable to predict the presence or absence of LPR, the total RFS score was highly suggestive of LPR in a patient with a score higher than 7. In addition, this scale is useful to evaluate the efficacy of treatment in patients with LPR. It was also found that reflux symptoms score was improved from 15 score (majority had this score; n=43) to 10 (n-18) at first follow up to 5 (n-16) at second follow up. (44) at third follow up and 0 (n-70) at the end of 4th follow up. Dawood et al accessed the clinical diagnosis of LPR in 78 patients presenting with voice related problems through assessment the agreement in correlation between main reflux symptoms and reflux physical laryngoscopical findings. It was found that the RSI was ranged from 13-30, with mean score 18.6, and the RFS was ranged from 7-19, with mean score 9.7. This study revealed a positive correlation between RSI and RFS, which was confirmed with both significant statistical analysis (p=0.001). (1) However some studies found that RFS and RSI have limited value, especially in symptomatic patients if used independently or in isolation (12, 13) while Keichner LN et al (14) detected a notable lack of agreement in reviewing video laryngoscopic examinations and implementing RFS scores on them.

In present study it was found that reflux finding score was improved from 10 score (majority had this score; n=28) to 7 (n=19) at first follow up to 6 (n=17) at second follow up, 2 (n=29) at third follow up and 0 (n=58) at the end of 4th follow up. The correlations between laryngeal findings, symptoms, and pH monitoring have been found to be weak. (15) It has been reported that findings normally associated with LPR may also be found among up to 86% of healthy controls, as shown in the report by Hicks et al. (16)

At present, the drugs most commonly used for the treatment of LPR are PPIs, which suppress acid production by directly acting on the H+-K+ ATPase of parietal cells. In present study it was found that majority of the patients have improved and showed all parameters within normal limit. Only one patient had CYST at lingual surface of Epiglottis. Mild oedema of Arytenoid was present in 48 patients and moderate oedema was reduced to 12 patients only. Mamillations of Interarytenoid region was seen in 70 patients. Only one patient had mild oedema of Post cricoid region and 21 patients had mild oedema of Mucosa overlying laryngeal framework. Only one patient had CYST at left ventricular of Epiglottis. Mild oedema of Arytenoid was present in 43 patients and moderate oedema was reduced 105 patients only. Mamillations of Interarytenoid region was seen in 56 patients. Only 1 patient had mild oedema of Mucosa overlying laryngeal framework. Although most patients show improvement of symptoms within 3 months, the resolution of symptoms and laryngeal findings generally takes 6 months. (3)

At 3rd follow up it was found that majority of the patients have improved and showed all parameters within normal limit. Only one patient had CYST at laryngeal surface of epiglottis. Mild oedema of Arytenoid was present in 35 patients and none had moderate oedema. Mamillations of Interarytenoid region was improved and was visible in none of the patients. In present study it was found that at the end of 4th follow up majority had all the parameters within normal limit. However, few patients had mild oedema of arytenoid (n=17) and 3 patients had mild oedema of aryepiglottis fold. Clinical evidence indicates that pharmacologic intervention should comprise a minimum of 3 months of treatment with PPIs administered twice a day, 30 to 60 minutes before a meal.

Significant failure rates have been reported when a single daily dose of the PPI was used, and most studies suggest adopting a regimen of two daily doses. (17) In the study of Park et al (18) a response to the regimen consisting of two daily doses of PPI was observed in 50% of the patients after 2 months of treatment, whereas only 28% of the patients receiving a single daily dose responded to treatment. In the single-dose

group, 54% of the patients who had not improved showed improvement of symptoms after an additional 2 months of treatment with two daily doses. After 4 months of treatment with two daily doses, an additional 22% of the patients had improved, resulting in a response rate of 70% after 4 months of treatment with two daily doses. Comparing laryngoscopic examination with the treatment given at baseline and 4th follow up, it was found that all the symptoms of epiglottis has come to normal at the end of 4th follow up as compared to baseline. Mild, moderate and severe oedema was reduced to almost normal at the end of 4th follow up. Relief was more with the combination of both prokinetic and PPI. Mamillations reduced to nil in all the groups at the end of 4th follow up. All the patients with mild oedema of aryepiglottis fold was reduced to within normal limit with the combination of both prokinetic and PPI as compared to individual drugs where few patients still had mild oedema. Thick endolaryngeal mucus was improved in all the groups. Overall combination of both prokinetic and PPI was able to improve the symptoms more effectively as compared to individual drug component. In one study, vocal lesions were suggested to represent more specific signs for LPR, with 91% specificity and 88% response to proton pump inhibitor (PPI) therapy. (18) Previous studies have reported that PPI therapy was more effective than H2R agonists and prokinetics for GERD, but none had investigated the efficacy of combined prokinetic and PPI therapy. Prokinetics in addition to PPI therapy may be a new treatment paradigm for PPI-non responsive patients. However, Ren et al (19) Marakhouski et al compared the efficacy and safety of PPI and prokinetic combination with PPI alone in reflux disease and found that Esophagitis reversal was observed in 92% patients group I vs 65.2% in group 2. Approximately, 83.3% patients in group I vs 43.3% patients in group 2 demonstrated full cupping of reflux symptoms at 8 weeks. Combined therapy resulted in significantly longer period of heartburn-free days (23 vs 12days on omeprazole). There were no safety concerns. (20) This is in line with the present study findings where combination therapy was found to be better as compared to individual drug in relieving the symptoms.

CONCLUSION

LPR is retrograde movement of gastric contents into the larynx, pharynx, and upper aerodigestive tract. LPR is a disease commonly diagnosed in otorhinolaryngology practice in the presence of a set of nonspecific laryngeal signs and symptoms. Symptoms were graded as reflux symptom index, RFS 13 or more was considered as significant on Pre-treatment visit. Retrosternal Burning was most common symptom. Symptoms of LPR started appearing during the initial disease course. Suspected cases went through Video Laryngoscopy with 70 degree and 90 degree Endoscope and findings like - Arytenoid Oedema, Vocal Fold Oedema, Mamillation, Posterior Commissure Hypertrophy, Thick Endolaryngeal Mucus Diffuse Laryngeal Oedema graded as REFLUX FINDING SCORE. RFS 7 or more is significant on Pre-treatment visit. Arytenoid Oedema followed by Interarytenoid Mamillations were most common Findings. Patients who were diagnosed as a case of LPR were randomly and equally divided into 3Groups [1- Proton Pump Inhibitors alone, 2- Prokinetics alone 3- Proton Pump Inhibitor and Prokinetic Combination] with 4 Regular Monthly Follow up till 4 months. Treatment with prokinetic and PPI combination were more effective in reducing the symptoms and edema of Laryngopharyngeal epiglottis and other parts. Oedema of Laryngopharyngeal organs were more common among those with age ≤50 years and duration of illness <3 months. Both reflux finding score and reflux symptoms score has very weak correlation with each other, however, both have been improved at 4th follow up. Combination therapy was more effective than Prokinetic or PPI alone in providing complete relief of reflux symptoms.

In this study, the abilities of the 70° and 90° telescopes to visualize 4 key regions of the vocal tract were evaluated and compared. Visualization of the subglottic area, the pyriform fossae, the anterior commissure, and the laryngeal surface of the epiglottis were attempted on subjects receiving both 70° and 90° telescopy. In conclusion, the 70° telescope successfully visualized the anterior commissure, the subglottic area, and the laryngeal surface of the epiglottis in a greater percentage of patients. This result may be of potential use to the clinical examiner selecting an instrument of choice.

REFERENCES

Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111:1313-1317.

Ford C N. Evaluation and management of laryngopharyngeal reflux. JAMA. 2005; 294:1534-1540.

Bove M J. Rosen C. Diagnosis and management of laryngopharyngeal reflux disease. Curr Opin Otolaryngol Head Neck Surg. 2006; 14:1:6-123.

Dobhan R, Castell D O. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. Am J Gastroenterol. 1993:88:25-29.

Achem SR, Robinson M. A prokinetic approach to gastroesophageal reflux disease. Dig Dis. 1998; 16:38-46. Treatment of gastroesophageal reflux disease. Dig Dis. 1998; 16:38-46.

Belafsky P C, Postma G N, Koufman J A. Validity and reliability of the reflux symptoms index (RSI) J Voice. 2002; 16:274-277.

Bove M J, Rosen C. Diagnosis and management of laryngopharyngeal reflux disease. Curr Opin Otolaryngol Head Neck Surg. 2006; 14:116-123.

Andrea Maria Campagnolo, Jaqueline Priston, Rebecca Heidrich Thoen, Tatiana Medeiros, Aida Regina Assunção. Laryngopharyngeal Reflux: Diagnosis, Treatment, and Latest Research. Int Arch Otorhinolaryngol 2014; 18:184-191.

Noordzij J P, Khidr A, Desper E, Meek R B, Reibel J F. Levine P A. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. Laryngoscope. 2002; 112:2192-2195.

Merati A L, Lim H J, Ulualp S O, Toohill R J. Meta-analysis of upper probe measurements in normal subjects and patients with laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2005; 114:177-182.

Dawood MR. A Clinical Diagnosis of Laryngopharyngeal Reflux in Patients with Voice related Problems via Correlation between Reflux Symptoms and Laryngoscopic Findings. Madridge J Otorhinolaryngol. 2018; 3(1): 55-59, doi: 10.18689/mjol-1000111

Watson NA, Kwame I, Oakeshott P, Reid F. Rubin JS. Comparing the diagnosis of laryngopharyngeal reflux between the reflux symptom index, clinical consultation and reflux finding score in a group of patients presenting to an ENT clinic with an interest in voice disorders: a pilot study in thirty-five patients. Clin Otolaryngol. 2013; 38(4): 329-333. doi: 10.1111/ coa.12113

Park KH, Choi SM, Kwon SU, Yoon SW, Kim SU. Diagnosis of laryngopharyngeal reflux among globus patients. Otolaryngol Head Neck Surg. 2006; 134(1): 81-85. doi: 10.1016/j.otohns.2005.08.025

Keichner LN, Home J, Lee L, Klaben B, Adam S, et al. Reliability of speechlanguage pathologist and otolaryngologist ratings of laryngeal signs of reflux in anasymptomatic population using the reflux finding score. J Voice. 2007; 21: 92-100. doi: 10.1016/j.jvoice.2005.09.004

Branski R C, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope. 2002;112:101-10

Hicks D M, Khandwala F. et al.Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. Laryngoscope. 2005; 115:1230-1238.

Leite L P, Johnston B T, Just R J. Castell D O. Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. Am J Gastroenterol. 1996; 91:1527-1531.

Park V, Hicks D M. Khandwala F. et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. Laryngoscope. 2005; 115:1230-1238.

Ren LH, Chen WX, Qian LJ, Li S, Gu M, Shi RH. Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol. 2014;20(9):2412-2419. doi:10.3748/wjg.v20.19.2412

Marakhouski KY, GA Karaseva2, DN Ulasivich2 and Y Kh Marakhousk. Omeprazole-Domperidone Fixed Dose Combination Omeprazole Monotherapy: A Phase 4, Open-Label, Comparative, Parallel Randomized Controlled Study in Mild to Moderate Gastroesophageal Reflux Disease. Clinical Medicine Insights: Gastroenterology Volume 2017; 10: 1-8: