A Prospective Study of Clinical Outcomes in Laryngopharyngeal Reflux Diseases Following Treatment with Proton Pump Inhibitors in a Tertiary Care Hospital in Kerala

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ABSTRACT

BACKGROUND

Laryngopharyngeal reflux (LPR) is found to be a common disease encountered in Otolaryngology practice. LPR presents clinically with symptoms of laryngeal irritation, frequent throat clearing, cough, and hoarseness of voice. The main diagnostic methods currently used are Fiber-optic laryngoscopy and in some centers pH monitoring. Proton pump inhibitors (PPIs) are used and found to be cost-effective and useful for the treatment of LPR. The main objective of this study was to study the effectiveness of PPIs in alleviating the symptoms assessed using Reflux Symptom Index (RSI) score and Reflux Finding Scores (RFS).

METHODS

A prospective study was carried out on 100 patients attending the ENT OPD of Government Medical College and Hospital, Thrissur, Kerala. Patients were evaluated for improvement in symptoms of Laryngopharyngeal reflux disease following use of proton pump inhibitors, using Reflux symptom index and Reflux finding scores using 70 degree / flexible nasopharyngolaryngoscopy. Patients with clinical findings of LPRD with RSI score > 13 and RFS score > 7 were given a standard treatment protocol followed in our ENT department using Tab. Pantoprazole 40 mg twice daily before food and the treatment response was assessed by proper follow up at 6 weeks and 12 weeks. On each follow up visit, improvement in RSI and RFS scores with Proton pump inhibitor therapy was assessed. Data collected was then tabulated and analysed.

RESULTS

The study was conducted in 100 patients, 59 % of whom were females and 41 % males. Mean RSI score changed from 18.9 at the beginning to 14.5 at 6 weeks of treatment and 9.0 at 12 weeks of treatment with Proton pump inhibitor. Mean RFS score changed from 10.7 at the beginning to 8.7 at 6 weeks of treatment and to 5.9 at 12 weeks of treatment. Comparison of mean Reflux Symptom Index and mean Reflux Finding Scores before and after treatment revealed improvement and the result was statistically significant (p value < 0.001).

CONCLUSIONS

The use of RSI and RFS scores in the assessment of PPIs at fixed intervals is cost effective and avoids time consuming and cost intensive examinations. These scores also help in early diagnosis and long term follow up of LPR patient. Fixed time interval PPI treatment significantly improved RSI and RFS scores in LPR patients. The mean RSI score changed from 18.9 at the beginning of treatment to 14.5 at 6 weeks after treatment (p value < 0.001) and 9.0 after 12 weeks of treatment; (p value < 0.001) The mean RFS score changed from 10.7 at the beginning of treatment to 8.7 at 6 weeks after treatment (p value < 0.001) and 5.9 after 12 weeks of treatment; (p value < 0.001).

KEYWORDS

Laryngopharyngeal Reflux, Reflux Symptom Index, Reflux Finding Score

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BACKGROUND

Laryngopharyngeal reflux (LPR) was found to be a common disease occurring in the general public with either acute or chronic symptoms.

Laryngopharyngeal reflux (LPR) occurs as a result of retrograde flow of stomach content to the larynx and pharynx resulting in contact between acid pepsin contents of the GIT with the mucosa[1] whereas Gastroesophageal reflux disease (GERD) is due to back flow of gastric contents into the oesophagus. Both the diseases are prevalent in general population and found to be epidemic.[2,3,4,5,6] As per the study of El-Serag,[2] the prevalence rates of both these diseases was found to have increased by 4% each year after 1976 with a corresponding increase in the prevalence of oesophageal cancer of 600 % since 1975 as per the records of the National Cancer Institute of the United States.[5] Similarly, a study by Altman et al reported a spurt of 500 % hike in visits of patients with complaints of LPR to the Otolaryngologist between 1990 and 2001.[3] In a study by Frazer AG, it was found that LPR was present in more than 50 % of patients with dysphonia.[7] In addition, LPR was included as an aetiological factor in the causation of certain laryngeal disorders like reflux laryngitis, subglottic stenosis, laryngeal carcinoma, laryngeal granulomas, contact ulcers, and vocal nodules.[8,9] Hence, patients of LPR should be diagnosed promptly. The treatment usually recommended for LPR includes dietary changes, losing weight, advice to quit smoking and alcohol and not going to bed immediately after taking food.[10] Restriction of food items including coffee, chocolate, aerated beverages, fat rich foods, tomato sauce, and red wine is also advised.[1,11] Presently the commonly used drugs in the treatment of LPR disease are PPIs. These drugs suppress acid production as they have direct action on H+-K+AT Pase of parietal cells. PPIs act not only by preventing the contact between the mucosa and acid contents but also by reducing the damage by the enzymatic activity of pepsin, which requires an acid medium for activation.[12] The treatment period required for clinical evidence of control was found to be a minimum of 3 months. Treatment schedule consisted of 40 mg Pantoprazole or an equivalent PPI, 30 to 60 minutes before a meal. The time interval was important as it provided the highest concentration of the drug during the period of stimulation of the proton pump by food consumption.[1,13] Although many LPR patients show relief from the symptoms within 3 months, resolution of laryngeal signs takes a minimum of 6 months symptoms.[1,13] These differences in response were also as a result of failure of studies standardizing the inclusion criteria, and grouping the patients according to severity of disease and absence of inclusion of adequate controls. In view of varying results observed following different protocols in the management of LPR disease, the present study was conducted to compare the RSI and RFS scores before and after treatment with PPIs at fixed time intervals. This study was conducted in the department of Otolaryngology Government Medical College Thrissur for a period of one year from December 2017 to November 2018. Prior to commencement, the study was approved by the ethical committee of the medical college. The study was conducted on 100 patients who presented to the ENT department with symptoms of Laryngopharyngeal reflux disease.

Aim of the Study

To conduct a clinical assessment of LPR disease by comparing the RSI and RFS scores before and after usage of PPIs in a tertiary care hospital in Kerala.

Objectives

To determine the effect of fixed time interval PPI treatment on RSI and RFS scores in LPR patients.

METHODS

Study Setting

Department of ENT, Govt. Medical College Thrissur.

Sample Size

Anagha Atul Joshi, Bhagyashree, Ganesh Chiplunker et al[10] conducted a study on 100 patients and found that the mean value of RFS at the time of evaluation was 11.84 with a standard deviation of 5.01

$$\mathrm{N} = \frac{(Z\alpha)^2 * (SD)^2}{d^2}$$

Z=1.96 for ɑ at 0.05
SD=5.01
d=absolute precision (value between 1-5)

$$= \frac{4 * (5.01)^2}{1 * 1} = 100$$

Hence Sample size: 100

Study Period

1 year**:** from December 2017 – November 2018.

Study Design

A Prospective study.

Participants

Patients consulted in department of ENT with features of Laryngopharyngeal reflux disease**.**

Inclusion Criteria

1. Patients aged above 18 years.
2. Patients presenting with symptoms and signs of LPRD (RSI > 13 and RFS > 7).

Exclusion Criteria

1. Children and adolescents below 18 years of age.

2. Patients suspected to have laryngeal malignancy.
3. Cases of paralytic dysphonia.

Methods

Patients reported in the department of ENT with clinical signs and symptoms of LPRD were included in the study. A written informed consent was obtained. Inclusion criteria and exclusion criteria were validated. The study was conducted with the principal investigator taking pertinent history from the patients recruited in the study on an individual basis. RSI Scores were calculated for all patients in the study. History included Reflux Symptom Index (RSI) score calculation, age, sex, occupation, tea or coffee intake, history of addictions, food habits, duration etc. RSI was a 9 item self-administered outcome tool.

RSI[4,5] Included

1. Hoarseness or problem with voice 0 1 2 3 4 5
2. Frequent clearing of throat 0 1 2 3 4 5
3. Excess throat mucus or post nasal drip 0 1 2 3 4 5
4. Difficulty swallowing food, liquids or pills 0 1 2 3 4 5
5. Coughing after having eaten 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 the throat or a lump in throat 0 1 2 3 4 5
9. Heart burn, chest pain, indigestion or stomach acid coming up 0 1 2 3 4 5

Each point was ranked from 0 (no problem) to 5 (severe problem). (0 - never, 1 - occasionally, 2 - sometimes, 3 - often, 4 - always, 5 - severe, affecting quality of life) RSI ranges from 0 to 45 (worst score). RSI > 13 is considered to indicate LPR.[6] The physical examination entailed a general examination and ENT evaluation with emphasis on Indirect Laryngoscopic examination. All patients are also evaluated with 70-degree rigid laryngoscope / Flexible nasopharyngolaryngoscopy. Findings were noted and scored according to Reflux Finding Score (RFS).

RFS[4,5] Included

1. Pseudo sulcus 0 absent, 2 present
2. Ventricular obliteration 0 none, 2 partial, 4 complete
3. Erythema or hyperaemia 0 none, 2 arytenoid only, 4 diffuse
4. Vocal cord oedema 0 none, 1 mild, 2 moderate, 3 severe, 4 obstructing (polypoidal)
5. Diffuse laryngeal oedema 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 0 absent, 2 present
8. Thick endolaryngeal mucus 0 absent, 2 present

RFS ranged from 0 (lowest possible) to 26 (highest possible). RFS > 7 have greater probability of having LPR.[6] Patients with clinical findings of LPRD with RFS score > 7 and RSI score > 13 were given a standard treatment protocol followed in the ENT department using Tab. Pantoprazole 40 mg twice daily before food.

Data Analysis

Data collected from each patient was entered in to an excel sheet after coding of variables and appropriate analysis was done with the help of SPSS 17 software. The collected data was subjected to suitable statistical analysis which included percentage analysis and graphical analysis. Results were presented as Mean ± SD values for continuous data and frequencies as numbers. Comparisons of post treatment changes in RSI and RFS values were done by paired t test. Chi-square test was used to analyze categorical data. A p value of 0.05 or less was considered for statistical significance.

RESULTS

Among the 100 patients whose data was analysed 33 belonged to the age group of 31 to 40 years, 28 belonged to the age group of 21 to 30 years, 18 were aged between 41 to 50 years and 15 were aged between 51 to 60 years. Patients aged below 20 years were 2 and patients aged above 60 years were 4 (Table 1). Among the 100 patients with LPR there were 41 males and 59 females with a male to female ratio of 1:1.43 (Table 1).

	Observation	Number
Age	< 20	2
	21 - 30	28
	31 - 40	33
	41 - 50	18
	51 - 60	15
	> 60	04
Gender	Male	41
	Female	59

Table 1. Distribution of Patient Sample based on their Age and Gender (n - 100).

The presenting complaints of the patients were analyzed using the RSI score chart and it was found that 52 % of the patients presented with complaint numbers 1, 3, 4 and 5, 25 % of the patients presented with complaint numbers 2, 4, 5, 6, 7, and 8. The remaining patients showed a combination of symptoms as shown in the table 2.

Complaints (Multiple)	No. of Cases	Percentage
1, 2, 3, 7, 8	7	7.0
1, 2, 4, 6	4	4.0
1, 2, 7, 9	4	4.0
1, 3, 4, 5	52	52.0
1, 3, 4, 5, 6, 7, 8	1	1.0
1, 3, 4, 7, 8	5	5.0
1, 4 ,7	1	1.0
2, 4, 5, 6 ,7, 8	25	25.0
5, 6, 8, 9	1	1.0
Total	**100**	**100.0**

Table 2. Distribution of Patients Sample based on RSI Score Chart of Presenting Complaints (n - 100)

The incidence of individual symptoms of the 100 patients was analysed and it was found that frequent clearing of throat was observed in 88 % of the patients, hoarseness or problem with voice was observed in 79 % of the patients,

sensation of something sticking in throat or lump in throat was observed in 74 % of the patients and heart burn, chest pain, indigestion or stomach acid coming up was observed in 65 % of the patients.

The symptoms of coughing after having eaten or after lying down was found in 42 % of the patients, difficulty swallowing food, liquid, or pills was found in 40 % of the patients and excess mucus in the throat was found in 31 % of the patients**.**

The RSI scores were calculated for all the patients at the time of examination and at fixed intervals of 6 weeks and 12 weeks. It was observed that none of them had RSI score between 0 and 12 at the beginning, 05 % at the end of 6 weeks and 74 % at the end of 12 weeks. It was observed that 53 % patients had RSI score between 13 and 15 at the beginning, 69 % at the end of 6 weeks and 26 % at the end of 12 weeks.

9 % of the patients had their RSI score between 16 and 20 in the beginning, 25 % at the end of 6 weeks and none at the end of 12 weeks. 12 % of the patients had their RSI score between 21 and 25, 1 % at the end of 6 weeks and none at the end of 12 weeks. 26 % of the patients had their RSI score between 26 and 30, none at the end of 6 and 12 weeks (Table 3). There was a shift in the RSI range as the treatment progressed in this study from the beginning to12 weeks period; (p value < 0.001), (Table 3).

RSI Range	At Beginning	AT 6 WKS Rx	AT 12 WKS Rx
0 - 12	-	5	74
13 - 15	53	69	26
16 - 20	9	25	-
21 - 25	12	1	-
26 - 30	26	-	-
Total	**100**	**100**	**100**

Table 3. Distribution of Sample with Corresponding RSI Score (n - 100)

x^2 = 249.8, P < 0.001, HS

The mean RSI score changed from 18.9 at the beginning of treatment to 14.5 at 6 weeks after treatment and 9.0 after 12 weeks of treatment; (p value < 0.001), (Table 4).

RSI	At Beginning	At 6 Wks of Rx	At 12 Wks of Rx	Mean Differences: Beginning to 6 Wks	Mean Differences: Beginning to 12 Wks	Mean Differences: 6 Wks-12 Wks
Mean ± SD	18.9 ± 4.9	14.5 ± 2.4	9.0 ± 2.6	4.4 ± 2.9	9.9 ± 2.6	5.5 ± 1.2
t value				15.49	37.63	46.44
P value				P < 0.001, HS	P < 0.001, HS	P < 0.001, HS

Table 4. Comparison of Changes in Mean RSI at Beginning to 6 Weeks and 12 Weeks of Treatment

RFS score of LPR disease patients was calculated based on clinical and endoscopic examination RFS score of LPR disease patients was calculated. It was found that among them, 56 % patients had RFS range between 11 and 15, 38 % had RFS range between 08 to 10, 06 % patients had RFS range between 16 and 20 (Table 5).

The presenting clinical findings observed in the patients were analysed using the RFS score chart and it was found that 52 % of the patients presented with the clinical findings numbered 3, 4, 5, 6, 25 % of the patients presented with the clinical findings numbered 1, 3, 4, 7 % patients presented with the clinical findings numbered 5, 6, 7 and 05 % of the patients presented with the clinical findings numbered 2, 3, 5, 6, 8 (Table 5).

Findings (Multiple)	No. of Cases	Percentage
1, 3, 4	25	25
1, 3, 4, 5, 6	1	1
2, 3, 5, 6, 8	5	5
2, 3, 5, 8	4	4
2, 4, 5	1	1
2, 5, 8	1	1
3, 4, 5, 6	52	52
5, 6, 8	7	7
5, 7, 8	4	4
Total	**100**	**100**

Table 5. Distribution of Sample Based on Examination Findings (n- 100)

On fiber-optic endoscopy examination of the larynx, erythema/hyperaemia of the larynx was found in 87 % of the patients, vocal cord oedema was found in 79 % of the patients, diffuse laryngeal oedema was found in 75 % of the patients, posterior commissure hypertrophy was observed in 65 % of the patients, pseudosulcus in 26 % of the patients, ventricular obliteration in 11 % and granuloma in 04 %. The RFS scores based on clinical findings of the larynx were calculated for all the patients at the time of examination and at fixed intervals of 6 weeks and 12 weeks. It was observed that none of them had RFS score between 0 and 7 at the beginning, 13 % at the end of 6 weeks and 90 % at the end of 12 weeks. It was observed that 38 % patients had RFS score between 8 and 10 at the beginning, 81 % at the end of 6 weeks and 10 % at the end of 12 weeks. 56 % of the patients had their RFS score between 11 and 15 in the beginning, 6 % at the end of 6 weeks and none at the end of 12 weeks; (p value < 0.001), (Table 6).

RFS Range	At Beginning	AT 6 WKS Rx	AT 12 WKS Rx
0 - 7	-	13	90
8 - 10	38	81	10
11 - 15	56	6	-
16 - 20	6	-	-
Total	**100**	**100**	**100**

Table 6. Distribution of Cases with Corresponding RFS Score at Beginning, 6 Weeks and 12 Weeks of Treatment

x^2 = 300.8, P < 0.001, HS

The mean RFS score changed from 10.7 at the beginning of treatment to 8.7 at 6 weeks after treatment and 5.9 after 12 weeks of treatment; (p value < 0.001), (Table 7).

RFS	At Beginning	At 6 Wks of Rx	At 12 Wks of Rx	Mean Differences: Beginning to 6 Wks	Mean Differences: Beginning to 12 Wks	Mean Differences: 6 Wks-12 Wks
Mean ± SD	10.7 ± 1.9	8.7 ± 1.5	5.9 ± 1.2	2.0 ± 0.9	4.8 ± 0.7	2.8 ± 0.6
t value				22.03	65.53	45.37
P value				P < 0.001, HS	P < 0.001, HS	P < 0.001, HS

Table 7. Comparison of Changes in Mean RFS at Beginning to 6 Weeks and 12 Weeks of Treatment

DISCUSSION

Laryngopharyngeal Reflux disease (LPR) is a frequently encountered disease in the outpatient departments of Ear, Nose, Throat Diseases. In spite of a large number of studies being conducted on LPR, controversies exist.[14] Though the disease itself was found to be a non-specific one, the combined symptoms and clinical findings are characteristic. Many of the studies have highlighted the varying degrees of laryngoscopic findings of LPR.[15] Presently the combination of symptoms and laryngoscopic finding is being used for diagnosis of LPR. Symptomatic improvement with empirical PPI helps in confirming the diagnosis. But in cases of failure in symptomatic improvement of LPR, further investigations should be conducted and factors other than reflux of acids need to be considered.[16] The other factors include pepsin and bile salts identified as causative agents; particularly pepsin, as it is capable of remaining stable intracellular in laryngeal tissues. Such pepsin gets reactivated by endogenous hydrogen ions derived from acid reflux or from diet.[17] The clinical data from the medical literature compares the empirical treatment of LPR with PPI therapy to placebo treatment. Such empirical therapy with PPIs for 2 to 3 months was recommended by many physicians and described in the medical literature as a cost-effective and useful for the initial diagnosis of LPR.[18] There always remained the difficulty in demonstrating the efficacy of PPIs. The present study was conducted in 100 patients with features suggestive of Laryngopharyngeal reflux presented in Government Medical College, Thrissur during the period of one year from December 2017 to November 2018. The results and observations of the above study have been interpreted and discussed as following. In the present study of 100 patients, age group varied between 18-66 years. 33 % of cases were in 31 - 40 age group, 28 % cases in 21 - 30 age group. Only 2 % cases were in < 20 age group and 4 % cases in > 60 age group. Mean age was 37.8. An important factor in sex distribution was the female predominance in study. Out of 100 cases, 59 % cases are females and 41 % males. In a study conducted by Pokharel M et al[19] about Laryngopharyngeal reflux in 82 patients, he also observed similar findings. Similar findings were observed in a study conducted by Park W et al;[20] in their prospective study evaluating optimal dose of proton pump inhibitor therapy in Laryngopharyngeal reflux disease. Koufman et al[21] conducted a study to find the prevalence of reflux in 113 patients with laryngeal and voice disorders. The study conducted by Pokharel M et al,[15] observed tea and coffee intake (in 60.97 %) as one of the main risk factor of Laryngopharyngeal reflux disease. Smoking and alcoholism were noted as risk factor in 22 % cases. Their study also had female predominance (65 %). In 1991, Jamie Koufman[21] estimated the LPR incidence at 10 % of a general ENT outpatient clinic. The main objective of study was to assess the treatment response in patients with Laryngopharyngeal reflux disease using Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). In the present study, at the beginning, 53 % cases had RSI score in range of 13 - 15, 26 % had score in range of 26 - 30, 12 % patients had score in range of 21 - 25 and 9 % patients had score in 16 - 20 range. At 6 weeks of treatment, 69 % cases had RSI score in 13 - 15 range, 25 % cases had score in 16 - 20 range, 5 % cases had score in 0 - 12 range and only 1 % had score in range of 21 - 25. At 12 weeks of treatment, 74 % cases had RSI score in 0 - 12 range and 26 % had score in 13 - 15 range. The main finding was that the mean RSI score changed from 18.9 at the beginning to 14.5 at 6 weeks of treatment and 9.0 at 12 weeks of treatment. (p value < 0.001). In a prospective study conducted for 2 years by Patigaroo SA et al[22] in 2011 similar findings were noted. Habermann W et al[23] in 2012 conducted a study in 1044 patients for a period of 20 months. They found mean RSI before proton pump inhibitor therapy was 12 which decreased to 3 after treatment (p value < 0.001). In the present study comparison of mean Reflux Symptom Index before and after treatment revealed improvement and the result was statistically significant (p value < 0.001). Thus, it is sure that proton pump inhibitor therapy has significant role in control of symptoms associated with Laryngopharyngeal reflux. But duration of treatment required is significantly longer. The study also assessed main findings among patients with Laryngopharyngeal reflux disease. In our study, 87 % patients had erythema / hyperaemia, 79 % had vocal cord oedema followed by diffuse laryngeal oedema in 75 % cases. Posterior commissure hypertrophy was noted in 65 % cases, pseudosulcus in 26 % cases and thick endolaryngeal mucus in 21 % cases. The least observed finding was granuloma, which was present in 4 % cases. In a study conducted by Lee et al[24] in 455 patients, the most common examination finding was posterior commissure hypertrophy in 89 % cases. This was followed by hyperaemia in 79 % cases and vocal fold edema. Other observations were similar to this study. The main observation in the present study was that the change in mean RFS score. Mean RFS score changed from 10.7 at the beginning to 8.7 at 6 weeks of treatment and to 5.9 at 12 weeks of treatment. Belafsky et al[25] in 2001 carried out a prospective study in 40 patients with a clinical diagnosis of LPRD and had similar observations. In a prospective study in 100 patients conducted by Anagha Atul Joshi et al[26] in 2017, for assessing treatment response in patient with LPR by using RSI and RFS scores, it was found that mean value of RFS improved after PPI therapy in a period of 2 to 6 months (p value < 0.001). They found that improvement started only after 2 months of treatment. Comparison of mean Reflux Finding Scores before and after treatment in our study revealed improvement and the result was statistically significant (p value < 0.001). Thus, proton pump inhibitor therapy has significant role in control of signs associated with Laryngopharyngeal reflux also.

CONCLUSIONS

The use of RSI and RFS scores in the assessment of PPIs at fixed intervals was cost effective and avoids time consuming and cost intensive examinations. These scores also help in early diagnosis and long term follow up of LPR patient. Fixed time interval PPI treatment significantly improved RSI and RFS scores in LPR patients. The mean RSI score changed

from 18.9 at the beginning of treatment to 14.5 at 6 weeks after treatment (p value < 0.001) and 9.0 after 12 weeks of treatment; (p value < 0.001). The mean RFS score changed from 10.7 at the beginning of treatment to 8.7 at 6 weeks after treatment (p value < 0.001) and 5.9 after 12 weeks of treatment; (p value < 0.001).

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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