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ORIGINAL ARTICLE

The Efficacy of PPI in the Treatment of Laryngopharyngeal Reflux

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ABSTRACT

BACKGROUND AND OBJECTIVES: Laryngopharyngeal reflux (LPR) is an inflammation affect large number of patients, it caused by the retrograde flow of gastric contents into the pharynx and larynx, causing a variety of symptoms. Therefore, the present study aimed to evaluate the efficacy of PPI in the treatment of LPR by both clinical & endoscopic follow up.

PATIENTS AND METHODS: This prospective observational study was conducted on 61 Consecutive patients attending the Otorhinolaryngology Clinic, Qena University Hospital from January 2018 to July 2018; patients were screened for symptoms of laryngitis. Patients were considered suitable for study if they had persistent laryngeal symptoms for at least 2 months. Laryngoscopic examination was performed using a flexible naso-pharyngoscope. The frequency and severity of patients' laryngeal symptoms were assessed by both reflux symptoms index & reflux finding score. All patients underwent an esophagogastroduodenoscopy before starting treatment, then 2 months and 6 months later (at the end of treatment). The degree of oesophagitis noted during EGD was graded according to Los Angeles classification.

RESULTS: This study included 61 patients with persistent laryngeal symptoms with their mean ages were 31.62 ± 5.16; 21 females (34.43%) and 40 males (65.57%) and their mean body mass index for male and female were 20 ± 4.2 and 23 ± 3.9 respectively. sensation of lump in throat was the most common symptoms found in 54 patient (88.52%) while breathing difficulties was the least presenting symptom detected in 21 patient (34.43%). Patients treated with pantoprazole 20 mg twice daily for 6 months. There was significant post treatment improvement of all presenting symptoms 2 months of regular therapy. (p = 0.0001), with complete disappearance of symptoms by 6 months of therapy. Erythema is the most common laryngeal finding detected in 54 patients (88.52%) However, pseudosulcus was present in 12 patients (19.67%). Marked improvement in reflux signs were detected at the end of 6 months of therapy, (p = 0.0001). Endoscopic partial ventricular obliteration, mild vocal cord edema, mild laryngeal edema and persistence of granuloma were still detected 6 months post regular acid suppression therapy. Follow up esophagogastroduodenoscopy after 2 and 6 months of regular treatment reviles completely apparent healthy mucosa.

CONCLUSIONS: Pantoprazole 20mg twice daily for 6 months was associated with significant improvement of laryngopharyngeal reflux symptoms and signs.

Key words: Proton Pump Inhibitors; Laryngopharyngeal Reflux; GERD

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INTRODUCTION

Laryngopharyngeal reflux has become a significant and increasingly prevalent disease seen in the otolaryngologist's office[1], estimated to be ranged from 18 to 80%[2,3]. Laryngopharyngeal reflux (LPR) is an inflammation caused by the retrograde flow of gastric contents into the pharynx and larynx, causing a variety of symptoms as: hoarseness of voice, globus sensation, excessive phlegm, frequent throat clearing and chronic cough, and the presence of GERD-attributed signs as erythema, edema, pachydermia, granuloma, or contact ulcer[4]. several studies have demonstrated multiple etiologic factors involved in the pathogenesis of laryngopharyngeal reflux disease (LPRD):Acidity of gastric juice alone may cause tissue damage at the upper airway level[5], but there is also other damaging factors (i.e. pepsin, bile salts, bacteria and pancreatic proteolytic enzymes) remain potentially damaging on PPI therapy and may have their damaging ability enhanced. Particularly, pepsin can damage all extragastric tissues at pH up to 6[6].

For the larynx, only three episodes a week has been shown to be associated with the development of significant disease, while for the esophagus, up to 50 reflux episodes a day is considered normal this is due to the more fragile laryngeal epithelium compared with the esophageal mucosa, also the larynx and pharynx are devoid of the acid clearance mechanism found in the oesophagus and thus is far more liable to peptic injury.so LPR patients don't complain of heartburn and regurgitation, predominantly upright (day time) refluxes not commonly postprandial with no prolonged esophageal acid clearance or dysmotility as those of GERD[1].

The diagnosis of LPR is a very difficult and its confirmation has several controversies most ENT surgeons use Laryngoscopic findings, especially edema and erythema to diagnose LPR[7]. But these laryngoscopic findings are not reliable from clinician to clinician and moreover one or more signs of laryngeal irritation are found in over 80% of healthy controls[8]. Moreover, it has been demonstrated that accurate clinical assessment of LPR is likely to be difficult because laryngeal physical findings cannot be reliably determined from clinician to clinician, and such variability makes the precise laryngoscopic diagnosis of LPR highly subjective[9].

Two useful self-administered tools, the Reflux Symptom Index[10] that help clinicians to assess the relative degree of LPR symptoms during initial evaluation and after treatment and the Reflux Finding Score[11], which appears to be useful for assessment the laryngoscopic finding and follow-up of LPR patients.

There are 3 approaches are described to confirming the presence of reflux: response of symptoms to behavioral and empirical medical treatment, demonstration of reflux events by multichannel impedance and pH monitoring studies, endoscopic observation of mucosal injury. Additional studies, including radiography, mucosal biopsy, esophageal manometer and spectrophotometric measurement of bile reflux, can provide information useful in targeting therapy[12].

The sensitivity and specificity of ambulatory pH monitoring as a means for diagnosing GERD in patients with extraesophageal reflux symptoms have been challenged[13].

Furthermore, the sensitivity of 24-h dual-probe (simultaneous esophageal and pharyngeal) monitoring has ranged from 50% to 80%[1].

Although there is some controversy regarding proton pump inhibitors efficacy, they considered the mainstay of medical treatment of LPR, other drugs such as H2-receptor antagonists, prokinetic agents, and mucosal cytoprotectants are also used in treatment[14].

PPIs are substituted benzimidazoles, they binds irreversibly to specific subunits on the outside surface of the luminal H^+/k^+ ATPase. As the final step in acid secretion involves activation of this enzyme, PPI therapy will reduce gastric acidity by inhibiting both basal and activated acid secretion[15].

There are Five PPIs are currently available: lansoprazole, omeprazole, pantoprazole, rabeprazole and esomeprazole, the first four compounds are racemic isomer mixtures, whereas esomeprazole includes only the S isomer of omeprazole. There are subtle structural differences between the various PPIs that may affect aspects of their antisecretory activity and clinical utility[16].

Once-daily dosing in the morning is more effective than dosing in the evening for all PPIs with respect to the suppression of intragastric acidity and daytime gastric acid secretion in particular. When higher doses are needed, these drugs should be given twice daily to achieve the optimal suppression of intragastric acidity. On twice-a-day dosing, inhibition of acid secretory capacity improves to 80% of maximally stimulated output[17].

PPIs are effective in the treatment of GERD, healing of erosive GERD and long-term resolution of acid-related symptoms[18].

Clinical data suggest that the optimal daily dose of PPIs for acute treatment of reflux-related symptoms and mucosal damage is about 30-40 mg. In less severe cases and in maintenance therapy doses of 10-20 mg daily may be sufficient with about 8 weeks of treatment is needed for the heal of erosive esophagitis[19,20].

All PPIs are very safe drugs with an adverse event profile not different to placebo with a low risk of clinically relevant drug-drug interactions[21,22].

Aim of study

To evaluate the efficacy of PPI in the treatment of LPR by both clinical and endoscopic follow up.

PATIENTS AND METHODS

This prospective observational study was conducted on 61 Consecutive patients attending the Otorhinolaryngology Clinic, Qena University Hospital from November 2017 till September 2018. The patients included in this study were presented to ENT department with persistent laryngeal symptoms of cough, sore throat, throat clearing, globus or hoarseness of voice for at least 2 months. The frequency and severity of patients' laryngeal symptoms were assessed by both reflux symptoms index & reflux finding score (Tables 1, 2).

Laryngoscopic examination was performed using a flexible naso-pharyngoscope during quiet respiration and free phonation by single experienced otorhinolaryngologist. A complete examination of the nose, pharynx and larynx was done.

Chest X-ray and ECG were done for patients with breathing difficulty to exclude chest problem and heart diseases.

All patients underwent an esophagogastroduodenoscopy (EGD) to confirm the presence of reflux using a video endoscope Olympus, GIF-XQ260 after sedation by IV midazolam 5 mg, before starting treatment, then 2 months and 6 months later (at the end of treatment). The degree of oesophagitis noted during EGD was graded according

to Los Angeles classification, were LA(0) = no esophagitis, LA (A) = ≥ 1 mucosal break ≤ 5 mm long not extending between mucosal folds, LA (B) = ≥ 1 mucosal break > 5 mm long not extending between mucosal folds, LA (C) = ≥ 1 mucosal break continuous between the tops of ≥ 2 mucosal folds, involving < 75% of the circumference and LA (D) = ≥ 1 mucosal break involving ≥ 75% of the circumference[23].

Inclusion Criteria

The primary entry criterion was laryngoscopically proven laryngitis, in the absence of concurrent infections or allergic causes of laryngitis for the last 2 month.

Exclusion criteria

Patients were excluded from the study if they had any of the following: past or present smoker, excessive alcohol consumption, chronic cough attributable to known chronic pulmonary or tracheobronchial disease, excessive voice users (e.g. singer, teacher), exposure to occupational or environmental inhaled pollutants, history of seasonal allergic rhinitis, previous neck or glottal surgery, tracheal intubation in the previous 12 months , use of inhaled corticosteroids and use of acid suppressor therapy over the last 60 days.

Basic data of patients including past medical history, occupation, alcohol consumption, cigarettes smoking, medications and known allergies were recorded.

Patients who were unable to or unwilling to participate in the study were also not considered. Patients who met the inclusion criteria were given a clear explanation of the study objectives and plan of the study and had given written informed consent to participate in the study. The study was approved by the hospital ethics committee.

Study design

This study was a prospective observational study for the efficacy of PPI in LPR.

Treatment schedule

All patients (regardless of whether they had typical GERD or Only LPR were treated with pantoprazole 20 mg twice daily taken on empty stomach for 6 months.

Follow Up

Patients were followed for 24 weeks, on two occasions first at 2 months and then at 6 months. On each follow up visit patients symptoms were evaluated with reflux symptom index, esophagogastroduodenoscopy and laryngoscopic findings scored with reflux finding score.

Statistical analysis

The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean ± SD). A two-tailed $p < 0.05$ was considered statistically significant. All analyses were performed using statistical package of social science SPSS 20.0 software.

RESULTS

The current study included 61 patients with persistent laryngeal symptoms of cough, sore throat, throat clearing, globus or hoarseness of voice for at least 2 months with their mean ages were 31.62 ± 5.16; 21 females (34.43%) and 40 males (65.57%) and their mean body mass index for male and female were 20 ± 4.2 and 23 ± 3.9 respectively.

Risk factors for development of gastroesophageal reflux disease were; reluxogenic food in 7 (11.48%), NSAIDs in 4 (6.56%) however no obvious risk factors were detected in 50(81.96%).

Esophagogastroduodenoscopy for all our included patients before starting acid suppression therapy reviled that ; 13 patients (21.31%) were Los-Angeles grade A, 40 patients (65.57%) were Los-Angeles grade B, 8 patients (13.12 %) were grade C and no patients are grade D (Table 3).

Follow up esophagogastroduodenoscopy after 2 and 6 months of regular treatment reviles completely apparent healthy mucosa.

In our study sensation of lump in throat was the most common symptoms, it was detected in 54 patient (88.52%) followed by frequent throat clearing in 48 patient (78.69%), excessive throat mucus 46 patient (75.41%), cough present in 40 patient (65.57%),26 (42.62%) of them complaint cough after eating or lying down &14 (22.95%) complain annoying cough, hoarseness of voice in 27 patient (44.26%) and least presenting symptoms was breathing difficulties in 21 patient (34.43%) as shown in table 4.

follow up of The presenting symptoms 2 months and 6 months after regular treatment with pantoprazole 20 mg twice daily reviled significant post treatment improvement of all presenting symptoms 2 months of regular therapy ($p = 0.0001$) and complete disappearance of symptoms by the end of 6 months therapy.

Erythema is the most common laryngeal finding in our study was present in 54 patients (88.52%) , 51 of them 83.31 were had diffuse erythema while 3 (4.92%) were arytenoid only followed by Diffuse edema represent in 52 patients (85.25%), 32 (52.46%) of which were moderate, 17 (27.87%) where severe and 3 (4.92%) where obstructed edema, followed by vocal cord edema in 50 patient representing mild edema in 9 patient (14.57%), moderate in 15(24.59%),severe in 20 (32.79%), obstructed in 6 (9.84%).

Posterior commissure hypertrophy presented in 40 patients, of them 11 (8.03%) were mild, 22 (36.07%) moderate, 4 (6.56%) severe &3 (4.92%) obstructed.

Ventricular obliteration were found in 34 patient, 22 (36.07%) of them completely obliteration and 12 (19.67%) were partial obliteration.

Both the granulation tissue and thick endolaryngeal mucosal were representing in 25 patients (40.98%) & finally pseudosulcus, which detected in 12 patients (19.67%) shown in table 5.

As regard, reflux symptom index, 2 months after therapy: (1) 11(18.03%) patients complained of hoarseness of voice with five patients were score 1 and six patients were score 2. (2) 15(24.59%)

Table 1 Reflux symptoms index.

Within the last 2 months how these symptoms affect you	**0 = no problem; 5 = severe problem**					
Hoarseness of voice	0	1	2	3	4	5
Frequent clearing of throat	0	1	2	3	4	5
Excess throat mucus or post nasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids or pills	0	1	2	3	4	5
Coughing after having eaten or after lying down	0	1	2	3	4	5
Breathing difficulties or chocking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations of something sticking in throat or a lump in throat	0	1	2	3	4	5
It ranges from 0 to 45 (worst possible score)						

Table 2 Reflux finding score.

Pseudo sulcus	0 Absent	2 present			
Ventricular obliteration	0 Absent	2 partial	4 compete		
Erythema /hypermia	0 Absent	2 arytenoid only	4 diffuse		
Vocal cord edema	0 Absent	1 mild	2 moderate	3 severe	4 polypoidal
Diffuse laryngeal edema	0 Absent	1 mild	2 moderate	3 severe	4 obstructing
Posterior commissure hypertrophy	0Absent	1 mild	2 moderate	3 severe	4 obstructing
Granuloma /granulation	0 Absent	2 present			
Thick endolaryngeal mucus	0 Absent	2 present			

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

Table 3 Characteristic data for all patients and the risk factors for GERD.

parameter	value
Number	61
Age (years) Mean ± SD	31.62 ± 5.16
Gender (N%)	
Male	40(65.57%)
Female	21(34.43)
BMI	
Male	20 ± 4.2
Female	23 ± 3.9
Risk factors (N%)	
Reluxogenic food	7(11.48%)
NSAIDs	4 (6.56%)
Nothing	50(81.96%)
Los-Angeles grade (N %)	
grade (A)	23 (37.70%)
grade (B)	30 (49.18%)
grade (C)	8 (13.12%)

Table 4 Presenting symptoms of all patients.

parameter	value
1) Hoarseness or problem with voice	27 (44.26%)
2) Frequent clearing of throat	48 (78.69%)
3) Excess throat mucus or postnasal drip	46 (75.41%)
4) Difficulty swallowing food, liquids or pills	15 (24.59%)
5) Coughing after having eaten or after lying down	26 (42.62%)
6) Breathing difficulties or chocking episodes	21 (34.43%)
7) Troublesome or annoying cough	14 (22.95%)
8) Sensations of something sticking in throat or a lump in throat	54 (88.52%)
9) Heartburn, chest pain, indigestion or stomach acid coming up	36 (59.02%)

patients had frequent throat clearing with three of them were score 1, ten were score 2 and two were score 3. (3) 7(11.48%) patients had excess throat mucus, all them were score 1. (4) 2(3.28%) patients had difficulty in swallowing, the two patients were score 2. (5) 3(4.92%) patients had coughing after eating or lying down, one patient were score 1 and the other were score 2. (6) 5(8.20%) patients complained of breathing difficulties or chocking episodes, three were score 2 and two were score 3. (7) 2(3.28%) patients complained of annoying cough, the two patients were score 2. (8) 13(21.31%) patients had foreign body sensation in the throat; five were score 1, five were score 2 and three were score 3. (9) 3(4.92%) patients complained of heart burn, the three patients were score 2 (Table 6).

At the same time marked improvement in reflux signs were detected at the end of 2 months and 6 months of PPI therapy.

Table 5 Presenting signs of all patients.

parameter	value
1) Pseudosulcus	12 (19.67%)
2) Ventricular obliteration	34 (55.74%)
3) Erythema/ hyperaemia	54 (88.52%)
4) Vocal cord edema	50 (81.97%)
5) Diffuse laryngeal edema	52 (85.25%)
6) Posterior commisure hypertrophy	40 (65.57%)
7) Granuloma / Granulation	25 (40.98%)
8) Thick endolaryngeal mucus	25 (40.98%)

Table 6 Reflux symptom index.

symptoms	Before treatment	After 2 months	P.value
Hoarseness or problem with voice			
1) Present	27 (44.26%)	11(18.03%)	
2) Absent	34 (55.74%)	50(81.97%)	0.02*
Frequent clearing of throat			
1) Present	48(78.69%)	15(24.59%)	
2) Absent	13(21.31%)	46(75.41%)	<0.0001***
Excess throat mucus or postnasal drip			
1) Present	46(75.41%)	7(11.48%)	<0.0001***
2) Absent	15(24.59%)	54(88.52%)	
Difficulty swallowing food, liquids or pills			
1) Present	15(24.59%)	2(3.28%)	
2) Absent	46(75.41%)	59(96.72%)	0.0036**
Coughing after having eaten or after lying down			
1) Present	26(42.62%)	3(4.92%)	<0.0001***
2) Absent	35(57.38%)	58(95.08%)	
Breathing difficulties or chocking episodes			
1) Present	21(34.43%)	5(8.20%)	0.0033**
2) Absent	40(65.57%)	56(91.80%)	
Troublesome or annoying cough			
1) Present	14(22.95%)	2(3.28%)	0.006**
2) Absent	47(77.05%)	59(96.72%)	
Sensations of something sticking in throat or a lump in throat			
1) Present	54(88.52%)	13(21.31%)	
2) Absent	7(11.48%)	48(78.69%)	<0.0001***
Heartburn, chest pain, indigestion or stomach acid coming up			
1) Present	36(59.02%)	3(4.92%)	
2) Absent	25(40.98%)	58(95.08%)	<0.0001***

However some of presenting signs were still detected 6 months post regular acid suppression therapy, partial ventricular obliteration were still detected in 8(13.11%) of included patients, mild vocal cord edema in 10 (16.39%) of patients, mild laryngeal edema in 7(11.48%)

Table 7 Reflux finding score.

Signs	Before treatment	After 2 months	P.value	After6 months	P.value
Pseudosulcus (N%)					
1) Present	12 (19.67%)	5(8.20%)		0(0%)	-------
2) Absent	49(80.33%)	56(91.80%)	0.146	61(100%)	
Ventricular obliteration					
1) Complete	22(36.07%)	0(0%)	<0.0001***	0(0%)	0.004**
2) Partial	12(19.67%)	19(31.15%)		8(13.11%)	
3) No	27(44.26%)	42(68.85%)		53(86.89%)	
Erythema/ hyperaemia					
1) Arytenoid only	3(4.92%)	11(18.03%)		0(0%)	-------
2) Diffuse	51(83.61%)	0(0%)	< 0.0001***	0(0%)	
3) No	7(11.48%)	50(81.97%)		61(100%)	
Vocal cord edema					
1) Mild	9(14.75%)	21(34.43%)		10(16.39%)	
2) Moderate	15(24.59%)	5(8.20%%)		0(0%)	0.0001***
3) Sever	20(32.79%)	0(0%)		0(0%)	
4) Obstructed	6(9.84%)	0(0%)	<0.0001***	0(0%)	
5) No	11(18.03%)	35(57.38%)		51(83.61%)	
Diffuse laryngeal edema					
1) Mild	0(0%)	32(52.46%)	<0.0001***	7(11.48%)	
2) Moderate	32(52.46%)	6(9.84%)		0(0%)	0.0001***
3) Sever	17(27.87%)	0(0%)		0(0%)	
4) Obstructed	3(4.92%)	0(0%)		0(0%)	
5) No	9(14.75%)	23(37.70%)		54(88.52%)	
Posterior commisure hypertrophy					
1) Mild					
2) Moderate	11(18.03%)	15(24.5%)		0(0%)	
3) Sever	22(36.07%)	9(46.56%)	0.0024**	0(0%)	--------
4) Obstructed	4(6.56%)	0(0%)		0(0%)	
5) No	3(4.92%)	0(0%)		0(0%)	
	21(34.43%)	42(68.85%)		61(100%)	
Granuloma/granulation					
1) Present	25(40.98%)	20(32.79%)	0.551	6(9.84%)	
2) Absent	36(59.02%)	41(67.21%)		55(90.16%)	0.0012**
Thick endolaryngeal mucus					
1) Present	25(40.98%)	7(11.48%)		0(0%)	------
2) Absent	36(59.02%)	54(88.52%)	0.0027**	61(100%)	

of patients, and persistence of granuloma in 6(9.84%) of them (Table 7).

DISCUSSION

Laryngoharyngeal reflux (LPR) has been reported in up to 10% of patients presenting to an otolaryngologist's office[1], and more than 50% of patients with hoarseness have been found to have reflux-related disease[24].

So in our study we use RSI & RFS to diagnose laryngopharyngeal reflex and assess response of patient to PPI and esophagogastroduodenoscopy (EGD) to confirm reflux. other studies done for response of RFS to PPI like studies of suhail et al[25], ***Belfasky & Postma***[11], ***Bilgen & Ogut***[26] the different that ***Belfasky &Postma*** and ***Bilgen & Ogut*** studies encountered pH monitoring to confirm reflux and ***suhail et al*** lack both EGD & PH monitoring.

In our study sensation of lump in throat was the most common symptoms in 45 patients (88.52%) followed by frequent throat

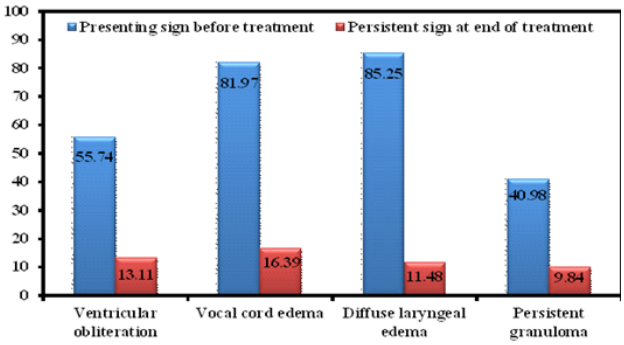

Figure 1 Presenting signs still detected 6 months post PPI therapy.

clearing in 48 patient (78.69%) then excessive throat mucus in 46 patient (75.41%) & cough in 40 patients (65.57%) this is correlated e Suhail et al who found Globus sensation in 74% of his patients followed by frequent clearing of throat in 64% of patients.

Other studies have also found globus pharyngeus as most common symptom like studies of ***Mesallam & Stemple***[31], ***Karkos& Yates***[28], ***Issing &Karkos***[29], while some studies have found other most common symptoms of LPR like throat burning (***Pieter Noordzij &Khidir***)[30], Hoarseness in 71% ***Koufman***[1], cough ***Eubanks et al.***[31], frequent clearing of throat ***Toros & Toros***[32].

Laryngeal erythema is the most common finding in this study represents 88.52% of our patients followed by diffuse edema in 85.25% of patients then focal cord edema in 81.97% of patients.

This is correlated with ***Suhail et al*** in his study who found erythema / hyperaemia to be the most common finding in 88% of patients[25]. Other studies have also found erythema as most common sign like studies ***Book and Rhee***[33], ***Mesallam and Stemple***[27], ***Karkos and Yates***[28] and ***Toros and Toros***[32]. Also ***Suhail et al***., found ventricular obliteration &posterior commissure hypertrophy to follow erythema in 88% and 76% of patients consecutively which is not correlated with our study as we found ventricular obliteration in (55.74%) of patients and posterior commissure hypertrophy in (65.57%).

In contrast also to our study other authors have noted other most common laryngoscopic signs like posterior commissure hypertrophy by ***Belfasky & Postma***[11], Partial ventricular obliteration by ***Tezer &Kockar***[34]. We noted Pseudo sulcus in only (19.67%) of our study group whereas ***Belfasky et al***.[35] found pseudo sulcus in 70% of study subjects and ***suhail et al*** found it in 50 % of his patients.

Unlike with GERD, response to PPI therapy in patients with LPR has been described as highly variable[36] this is in part because LPR requires more aggressive and prolonged therapy than GERD[37]. Clinical trials have failed to quell the controversy because studies have had different inclusion criteria, failed to stratify populations based on LPR severity, lacked adequate controls, and, often, used inappropriate dosage or duration of therapy[12].

In our study all patients were treated with pantoprazole 20 me twice daily taken on empty stomach for 6months all patients show significant post treatment improvement of all presenting symptoms on 2 months of regular therapy and complete disappearance on the 6th month of therapy. Also marked improvement in reflux signs were detected at the end of 2 months and 6 months of PPI therapy with significant ($p = 0.0001$).

However some of presenting signs were still detected 6 months post regular acid suppression therapy, partial ventricular obliteration were still detected in 8(13.11%) of included patients, mild vocal cord edema in 10(16.39%) of patients, mild laryngeal edema in 7(11.48%)

of patients, and persistence of granuloma in 6 (9.84%) of them.

This correlated with ***Serage el al***[38] in their randomized, double-blind, placebo-control trial of lansoprazole (30 mg twice daily) for 3 months found a significantly greater proportion (50%) of lansoprazole treated subjects that reported a complete symptom response.

And with ***Noordzij et al***[39] in their placebo-control trial of 2-month treatment with omeprazole (40 mg twice daily) found significantly greater improvement in hoarseness and throat clearing in the omeprazole group, but failed to show significantly greater improvement in overall laryngo-pharyngeal symptoms but their study included only patients with abnormal pH probes and specifically instructed all patients not to comply with lifestyle modification for reflux. While ***Havast et al***[40] in another randomized placebo-control study of lansoprazole (30 mg twice daily) also found no significant benefit from PPI treatment over placebo for composite laryngeal symptoms. Also ***Steward et al***[41] study suggested that lifestyle modification for 2 months with or without proton pump inhibitor therapy, significantly improves reflux related symptoms in patients with chronic laryngo-pharyngitis.

In our study we have persistent signs as granuloma, partial ventricular obliteration and mild edema, that still detected 6 months post regular PPI therapy.

So these patients may be benefit from adding anti-inflammatory drugs

Coclusion: six months proton pump inhibitors are efficient therapy for management of laryngeopharyngeal reflux (LPR) with significant improvement in all symptoms and signs. Further studies are needed to evaluate the role of addition of anti-inflammatory drugs for patients with persistent signs despite treatment with PPI therapy.

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