IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 4 Ver. III (Jul – Aug 2018), PP 54-61
www.iosrjournals.org

Effect of Proton Pump Inhibitors in the Treatment of Laryngopharyngeal Reflux

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Abstract: *To study the effect of proton pump inhibitors in the treatment of laryngopharyngeal reflux by means of 'Reflux symptom index' and 'Reflux finding score'*
A prospective observational study was carried out in Rajah Muthaiah Medical college and hospital. And a total of 20 patients were enrolled for the study to investigate the effect of proton pump inhibitors in the management of laryngopharyngeal reflux using a predesigned format out of which 20 of them completed successfully. Total number of patients included in the study were 20. females 13patients and their percentage is (65%) , males 7patients which gives (35%). Age of the patients varied from 0 to 70 years. No patient was less than 20 years of age.the majority of subjects affected in our study were age group 31 to 40 years forming about 40% and the age group of 41 to 50 years forming about 30% of the study group.
Keywords*: laryngopharyngeal reflux, proton pump inhibitor, ENT (ears, nose and throat)*

Date of Submission: 20-07-2018 Date of acceptance: 04-08-2018

I. Introduction

Laryngopharyngeal reflux (LPR) is an extraesophageal variant of gastroesophageal reflux disease that affects the larynx and pharynx [3]. LPR refers to retrograde flow of gastric contents to the upper aero-digestive tract. Supraesophageal reflux, extraesophageal reflux, various terms for LPR reflux laryngitis, laryngeal reflux, gastropharyngeal reflux, pharyngoesophageal and atypical reflux [1].

CAUSES

Stomach acid backs up into the back of the pharynx or larynx. It can cause inflammation, irritation and changes in the larynx. [3]

- Narrowing of the area below the vocal cords
- Contact ulcers
- Recurrent ear infections from problems with Eustachian tube function
- Lasting buildup of middle ear fluid
- Smoking.
- Obesity.
- Immediate is sleeping after meals.
- Alcohol consumption.
- Missing of breakfast.
- Bananas, tomatoes, citrus fruits, dairy products, chocolate, coffee, tea, soft drinks that contain caffeine may aggravate reflux.

SIGNS AND SYMPTOMS

The reactive airway *Symptoms in infants and children may include following*:

- Hoarseness
- Asthma
- Noisy breathing or pauses in breathing.
- Trouble feeding, spitting up, or inhaling food
- Trouble gaining weight

LPR, adults may have included:

Saliva that is swallowed neutralizes acid in the esophagus, but does not do the same for acid that gets into the voice box area. Patient with LPRD often has throat symptoms because the lining of the throat is more sensitive to irritation cause by acidic or non acidic stomach fluids. Patients with LPRD usually have one or more of the following symptoms include:

- Chronic intermittent hoarseness
- Frequent laryngitis
- Throat clearing
- Cough
- Trouble swallowing
- A feeling like "something is in the throat that I can't swallow" excessive throat mucus.
- post-nasal drip
- spasms of the vocal cords causing noisy breathing of difficulty breathing

RISK FACTORS

- Certain habits and conditions can contribute to LPR;
- Drinking caffeinated beverages
- Eating before bedtime
- Eating foods that are high in fat, tomato-based, or spicy
- Lying down after eating
- obesity
- Alcohol use
- Smoking
- Wearing tight clothing.

PATHOPHYSIOLOGY

The etiologies of reflux events that occur with LPR are largely unknown, although UES dysfunction has been hypothesized as a possible factor. Although esophageal dysmotility and lower and lower esophageal sphincter dysfunction play important role in GERD, they appear to have less of a role in LPR. Furthermore, manometry, including the pharynx and USE, demonstrates that patients with LPR often have normal esophageal motility. Unlike GERD, which primarily involves supine (noctural) reflux events, LPR reflux occurs frequently in the upright position. The reflux events in LPR also tend to be brief relative to the prolonged events that occur with GERD. The laryngeal damage that occurs in LPR is not caused by acid alone, but it requires both acid and activated pepsin, and it must be remembered that pepsin remains active over a pH of 5.0. When compared to the esophageal mucosa is injured with much lower levels of acid/pepsin exposure. It has been accepted that the extrinsic defense mechanisms between the laryngopharynx and the esophagus are markedly different, with the latter having much more resistance to acid peptic exposure. In fact, the *intrinsic* defense mechanisms of the laryngeal and esophageal mucosa are different as well. For example, one of the carbonic anhydrase(CA) isoenzymes, CA III, has been shows to have increased expression in the esophageal mucosa in response to refluxate exposure, whereas the larynx demonstrate a depletion of CA III after chronic reflux exposure. Furthermore, although esophageal mucosal response to acid/pepsin exposure appears to often be readily reversible, laryngeal mucosa can easily be damaged irreversibly.

II. Diagnosis

Videoscopy (Videolaryngoscopy)

The laryngoscopic findings used for the diagnosis of reflux are non specific signs of laryngeal irritation and inflammation. Thelaryngeal exam identifies edema and erythema, particularly in the posterior region. These are the main findings used by various investigators for the diagnosis of LPR. Granulomas, contact ulcers, and pseudosulcus are also common findings.[2] 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 fiberopticlaryngoscopy.[2]

This scale evaluates eight items that comprise the most common laryngoscopic findings in patients with LPR: subglottic edema; ventricular obliteration; erythema or hyperemia; vocal foldedema; generalized laryngea ledema; 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 than7. In addition, this scale is useful to evaluate the efficacy of treatment in patients with LPR (►Table 1).[2]

Table 1: Reflux finding score (2)

REFLUX FINDING SCORE	
1.Pseudosulcus	0 = Absent 2 = Present
2. Ventricular obliteration.	0 = None 2 = Partial 4 = Complete
3. Erythema/Hyperaemia.	0 = None 2 = Arytenoids only. 4 = diffuse
4. Vocal cord edema.	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Obstructing
5. Diffuse laryngeal edema.	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Obstructing
6. Posterior commisure 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

Table 2: REFLUX SYMPTOM INDEX 1

Reflux symptom index	0 = No problem 5 = Severe problem					
1. Hoarseness or voice problem	0	1	2	3	4	5
2. Throat clearing.	0	1	2	3	4	5
3. Excess mucus or post nasal drip	0	1	2	3	4	5
4. Difficulty in swallowing solids, fluids.	0	1	2	3	4	5
5. Coughing after eating or lying down.	0	1	2	3	4	5
6. Breathing difficulties or choking episodes.	0	1	2	3	4	5
7. Annoying cough.	0	1	2	3	4	5
8. Sensation of a lump or foreign body in the throat.	0	1	2	3	4	5
9. Burning, heart burn, chest pain, indigestion or stomach acid coming up.	0	1	2	3	4	5
	Total					

RSI (Reflux Symptom Index) for the assessment of symptoms in patients with reflux disease that can be completed in less than 1 minute. The scale for each individual item ranges from 0 (noproblem) to 5 (severeproblem), with a maximum score of 45
(►Table2). The authers concluded that the questionnaires hows high reproducibility and validity for the diagnosis of reflux if an RSI score > 13 is defined as abnormal2.

TREATMENT

Proton-pump inhibitors (PPIs) are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available. The elimination half-life of PPIs ranges from 0.5 to 2.0 hr, but the effect of a single dose on acid secretion usually persists up to three days. This is because of accumulation of the drug in parietal cell canaliculi and the irreversible nature of proton pump inhibition Omeprazole, Lansoprazole, Dexlansoprazole, Esomeprazole, Pantoprazole, Rabeprazole and Ilaprazole are the commonly used proton pump inhibitors.[1]Omeprazole has the highest risk for hepatic basedinteractions, and rabeprazole and pantoprazole appear to have the lowest risk. The

rate of omeprazole absorption is decreased by concomitant food intake. In addition, the absorption of lansoprazole and esomeprazole is decreased and delayed by food. Pantoprazole and lansoprazole are approved for intravenous administration.[1]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.[1]

The PPI binds irreversibly to a hydrogen/ potassium ATPase enzyme (Proton pump) on gastric parietal cells and blocks the secretion of hydrogen ions, which combine with chloride ions in the stomach lumen to from gastric acid. PPIs block secretion of hydrogen ions into the stomach.[4]

PANTOPRAZOLE
DOSE: 40mg orally once a day.
ADR: Headache, Abdominal pain, Facial edema, Chest pain, Diarrhea, Constipation.
Mechanism of action : PPI; binds to H+/K+ exchanging ATPase (proton pump) in gastric parietal cells, resulting in blockage of acid secretion.

ABSORPTION:
Bioavailability: 77% (PO: neither food nor antacids alters bioavailability)
Peak plasma time: 2.8 hr (PO); at end of infusion (IV)

DISTRIBUTION: Protein bound: 98%
Volume of Distribution: 11-24L

METABOLISM: Metabolized extensively by hepatic P450 enzyme CYP2C19; second pathway through CYP3A4.

ELIMINATION:
Half-life: 1 hr; increased to 3.5-10hr with CYP2C19 deficiency
Renal clearance: 0.1 L/hr/kg
Total body clearance: 7.6-14 L/hr
Excretion in urine (71%); feces (18%)
Oral administration
Switch IV patients to PO as soon able to take tablets
Administer before meals
IV compatibilities
Y-site : midazolam, zinc solution

NON PHARMACOLOGICAL MANAGEMENT
- Avoid alcohol
- Avoid tight-fitting cloth around waist
- Cease eating at least 3 hours prior to before sleep
- Consider chewing gum to increase saliva and neutralize acid
- Elevate the head of the bed approximately 4-6 inches
- Limit intake of alcohol, caffeine, chocolate, fats, citrus fruits-or tomato based foods, spicy foods, carbonated beverages, mints.
- Reduce weight, if necessary.
- Quit smoking.

MONITORING

The symptoms and signs of LPR may be complex. The clinicians will identify limitations of patient symptoms (RSI) and diagnosing LPR have motivated other investigators to quantify laryngeal findings attributed to reflux (RFS). RFS of more than 7 and RSI of more than 13 are associated with high likelihood of LPR. Our patients of LPR responded within 4^{th} week of therapy, though laryngeal signs took more time to resolve, about 10^{th} week. RFS will be monitored by physicians by the help of laryngeoscopy. [1]

PATIENT COUNSELLING
- Don't drink caffeinated beverages
- Eat small well balanced meals.
- Don't take foods that are high in fat, tomatos -based, or spicy

- Take medicine before 30 minutes of food intake.
- Avoid medication that can aggravate heart burn
- don't skip medicines.
- Alcoholism and Smoking
- Manage psychological stressors.
- Don't wearing tight model clothing
- Elevate the head of the bed 6-8 inches
- Wait 2 – 3 hrs after last meals before lying down

III. Observations And Results

PERCENTAGE DISTRIBUTION OF REFLUX SYMPTOM INDEX

Table 3 Percent distribution of symptom (RSI)

Symptom	Total no of patients	Percentage
Burning, heart burn, chest pain, indigestion or stomach acid coming up.	20	100
Throat clearing.	18	90
Sensation of a lump or foreign body in the throat.	18	90
Coughing after eating or lying down.	18	90
Annoying cough.	18	90
Breathing difficulties or choking episodes.	17	85
Difficulty in swallowing solids, fluids.	15	75
Hoarseness or voice problem	14	70
Excess mucus or post nasal drip	13	65

Burning, heart burn, chest pain, indigestion or stomach acid coming up was the most common symptom present in 100% of patients followed by Throat clearing in 90% and Sensation of a lump or foreign body in the throat 90%, Coughing after eating or lying down 90%, Annoying cough 90%, Breathing difficulties or choking episodes 85%, Difficulty in swallowing solids, fluids 75%, Hoarseness or voice problem 70%, Excess mucus or post nasal drip 65 of patients (**Table 3**).

PERCENTAGE DISTRIBUTION OF REFLUX FINDING SCORE.

Table 7
Percentage distribution of signs (Reflux finding score)

Symptoms	Number of patients	Percentage
Erythema/Hyperaemia.	18	90
Ventricular obliteration.	17	85
Vocal cord edema.	16	80
Posterior commisure hypertrophy.	15	75
Diffuse laryngeal edema.	14	70
Thick endolaryngeal mucus.	13	65
Pseadosulcus	11	55
Granuloma/ granulation.	11	55

Most common laryngeal finding was erythema/hyperaemia 90%,Ventricular obliteration 85% followed Vocalcord edema 80% and posterior commisure hypertrophy75%, Pseudosulcus and Granuloma was seen in 11 patient's (**Table 5**).

CHANGES OF RSI WITH PROTON PUMP INHIBITORS.

Table 4 Changes of RSI with PPI

Age group	No of patients	Pre-treatment (RSI)	Post- treatment after 4 weeks	Post-treatment after 10 weeks
0-10	0	-	-	-
11-20	0	-	-	-
21-30	3	23	18	10.3
31-40	8	21.33	16	9.5
41-50	6	25.16	18	10.3
51-60	1	22	13	3
61-70	2	26	19	11
Total	20	23.498	16.800	8.820

Mean RSI of all patients was 23. 50 before treatment with proton pump inhibitors. After 4 weeks of therapy with PPI mean RSI decreased to 16.80 and after 10 weeks of PPI therapy mean RSI dropped to 8.82 (**Table 4**). Significant change in RSI occurred after 10 weeks of therapy in total and in all age groups.

T-test for RSI Pre treatment vs post-treatment 4th week
Normality Test: Passed (P = 0.255)
Equal Variance Test: Passed (P = 0.555)

Table 5

	N	Missing	Mean	Std Dev	SEM
Pre- treatment	7	2	23.498	2.013	0.900
Post- treatment 4th week	7	2	16.800	2.387	1.068
Difference 6.698					

t = 4.796 with 8 degrees of freedom. (P = 0.001)

95 percent confidence interval for difference of means: 3.477 to 9.919

The difference in the mean values of the two groups is greater than would be expected by chance; there is a statistically significant difference between the input groups (P = 0.001).
Power of performed test with alpha = 0.050: 0.988

T-test Pre treatment vs post-treatment 10th week
Normality Test: Passed (P = 0.258)
Equal Variance Test: Passed (P = 0.628)

Table 6

	N	Missing	Mean	Std Dev	SEM
Pre- treatment	7	2	23.498	2.297	0.900
Post- treatment 10th week	7	2	8.820	3.297	1.474
Difference 14.678					

t = 8.497 with 8 degrees of freedom. (P = <0.001)

95 percent confidence interval for difference of means: 10.694 to 18.66

The difference in the mean values of the two groups is greater than would be expected by chance; there is a statistically significant difference between the input groups (P = <0.001).Power of performed test with alpha = 0.050: 1.000

CHANGES OF RFS WITH PROTON PUMP INHIBITORS

Changes of RFS with PPI				
Age group	No of patients	Pre-treatment (RFS)	Post- treatment after 4 weeks	Post-treatment after 10 weeks
0-10	0	-	-	-
11-20	0	-	-	-
21-30	3	13	9	4.3
31-40	8	12	8.5	3
41-50	6	13	8	4
51-60	1	12	8	4
61-70	2	15	9.5	4
Total	20	13.000	8.600	3.860

Mean RFS of the patients was 13.00 before treatment with proton pump inhibitors. After 4 weeks of therapy with PPI mean RFS decreased to 8.60 and after 10 weeks of PPI therapy mean RFS dropped to3.86 (**Table 8**) which was statistically significant. There was slight response after 4 weeks of therapy in physical findings in all age groups and significant response after 10 weeks of therapy in total and in all age groups.

T-test for RFS Pre-treatment vs Post-treatment 4th week

Normality Test: Passed (P = 0.295)
Equal Variance Test: Passed (P = 0.075)

Table 9

	N	Missing	Mean	Std Dev	SEM
Pre- treatment	7	2	13.000	1.225	0.548
Post- treatment 4th week	7	2	8.600	0.652	1.292
Difference 4.400					

t = 7.091 with 8 degrees of freedom. (P = <0.001)

95 percent confidence interval for difference of means: 2.969 to 5.831

The difference in the mean values of the two groups is greater than would be expected by chance; there is a statistically significant difference between the input groups (P = <0.001).Power of performed test with alpha = 0.050: 1.000

T-test for RFS Pre-treatment vs Post-treatment 10th week
Normality Test: Passed (P = 0.102)

Equal Variance Test: Passed (P = 0.268)

Table 10

	N	Missing	Mean	Std Dev	SEM
Pre- treatment	7	2	13.000	1.225	0.548
Post- treatment 10th week	7	2	3.860	0.498	0.223
Difference 9.140					

t = 15.458 with 8 degrees of freedom. (P = <0.001)

95 percent confidence interval for difference of means: 7.777 to 10.503

The difference in the mean values of the two groups is greater than would be expected by chance; there is a statistically significant difference between the input groups (P = <0.001).Power of performed test with alpha = 0.050: 1.000

IV. Discussion

The most common symptoms of LPR are hoarseness, globus pharyngeus, dysphagia, cough, chronic throat clearing, post nasal drip and sore throat. These symptoms are often intermittent or chronic intermittent. However, these symptoms are not specific for LPR, and may becaused by rhinitis, asthma, laryngeal cancer, and many other pathologic conditions. The most common manifestation of LPR is reflux laryngitis with or without In addition, Erythema/Hyperaemia, Ventricular obliteration, vocal cord edema, Posterior commisure hypertrophy, Diffuse laryngeal edema, Thick endolaryngeal mucus, pseudosulcus, granulation or granuloma formation

Females (65%) outnumbered the males (35%) in the current study. most common symptom in the study on LPR patient's Burning, heart burn, chest pain, indigestion or stomach acid coming up was the most common symptom present in 100% of patients followed by Throat clearing in 90% and Sensation of a lump or foreign body in the throat 90%, Coughing after eating or lying down 90%, Annoying cough 90%, Breathing difficulties or choking episodes 85%, Difficulty in swallowing solids, fluids 75%, Hoarseness or voice problem 70%, Excess mucus or post nasal drip 65 of patients (**Table 3**).

We used RSI and RFS to assess the role of PPI. We found significant improvement in both symptoms and signs after 10 weeks of PPI therapy. Symptomatic improvement was obvious after 4 week of therapy but laryngeal signs took 10 week to show improvement. Overall physical finding did not change significantly after 4 weeks of therapy but it changed so after 10 weeks. First study to use PPI was by Kamel who used omeprazole. In the study we are used pantoprazol 40mg.

The PPIs are commonly given before meals in most of the studies. Twice-daily dosing is usually employed to better control both nocturnal and daytime esophageal acid exposure. In other studies include omeprazole 20 mg twice daily, esomeprazole 20 mg twice daily, rabeprazole 20 mg twice daily as compared to higher doses used in other studies. Our study after Pantoprazole (PPI) therapy found dramatic response in signs and symptoms and showed unexpectedly 100% response rate with PPI therapy. Overall we observed in patients that single dose proton pump inhibitor for treatment of laryngopharyngeal reflux resulted in good response rate and treatment must be continued for at least 10 weeks. Laryngeal signs may take more time to resolve as also reported in literature.

Our study is in accordance with many studies reported in literature like Metz and Childs in a study of 10 patients of reflux laryngitis who were treated by PPI (20mg omeprazole) for 1 month found a symptomatic improvement in, Shaw and Searl in a study of 68 patients of reflux laryngitis who were treated with improvement in 60% with the exception of granuloma formation, Jasperson and Weber who demonstrated complete (100%) symptom free healing of LPR after a 4 weeks treatment with 40 mg omeprazole per day as also demonstrated in our study.

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Nkusi Steven "Effect of Proton Pump Inhibitors in the Treatment of Laryngopharyngeal Reflux." IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.4 (2018): 54-61