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A randomised control study comparing efficacy and safety of Rabeprazole monotherapy Vs Rabeprazole and Domperidone combination in patients with Laryngopharyngeal reflux disease at a tertiary care centre.

Kiran Thimmarayappa,[1] Musarrat Feshan,[2] Preetham A P [3]
1- Resident, Department of ENT, Southern Railway Head-quarters Hospital, Perambur, Chennai.
2- Head of the Department of ENT, Southern Railway Head-quarters Hospital, Perambur, Chennai.
3- Additional chief health director, Department of ENT, Southern Railway Head-quarters Hospital, Perambur, Chennai.
Corresponding Author: Dr. Kiran T

Abstract
Background- *Laryngopharyngeal reflux (LPR) disease is a common entity encountered in routine otolaryngologic practice. It has a variable presentation posing a difficulty in diagnosis and treatment. Proton pump inhibitors (PPI) are considered as both a diagnostic and therapeutic approach for LPR.*
Methodology- *In the present, randomized open label study, 54 patients with LPR were evaluated to determine efficacy and safety of Rabeprazole monotherapy vs Rabeprazole and Domperidone combination therapy. The patients were divided into 2 groups of 27 each. Group A received Rabeprazole 20mg + Domperidone 30mg and group B received Rabeprazole 20mg once daily for 4 weeks. The patients were assessed by flexible laryngoscopy before and after 4 weeks. Reflux symptom index (RSI) and Reflux finding score (RFS) were used to assess the outcomes.*
Results- *The total number of patients were 54 and the mean age was 40.37 years with majority in the age group of 30-49 years (n= 34) followed by < 30 years (n= 10) and there was mild male preponderance (53.7 %).*
At baseline, the mean RSI score was 15.19 and 15.11 which significantly reduced to 7.59 and 8.26 after 4 weeks in group A and group B respectively. Statistically significant improvement of RSI was observed in group A when compared to group B, with p value of 0.003 after 4 weeks. At baseline, mean RFS was 8.19 and 8.41 which significantly reduced to 6.56 and 7.07 after 4 weeks in group A and group B respectively, however there was no significant difference between the groups was observed at end of 4 weeks. Mild headache and transient diarrhea were the adverse effects noted in this study.
Conclusion- *Overall we observed that Rabeprazole with Domperidone is a better choice for improvement in symptoms of LPR and both the drugs are efficacious and well tolerated.*
Keywords- *Laryngopharyngeal reflux (LPR), Proton Pump Inhibitors (PPI), Rabeprazole, Domperidone, Reflux Symptom Index (RSI), Reflux Finding Score (RFS)*

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I. Introduction:

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition of the upper aero-digestive tract tissues related to the direct and indirect effect of gastric or duodenal content reflux, which induces morphological changes in the upper aero-digestive tract.[1] Jamie A Koufman coined the term Laryngopharyngeal reflux disease.[2] The most common symptoms of LPR are globus sensation, hoarseness of voice, throat clearing, postnasal drip, and excess throat mucus.[1] The LPR findings commonly seen are posterior commissure hypertrophy, laryngeal/arytenoid inflammation, and endolaryngeal mucus. [3-6] The prevalence of LPRD is high, [7, 8] it adds significant morbidity to patients and also poses a diagnostic challenge to otolaryngologists.

Proton pump inhibitors (PPIs) with or without prokinetics, antacids, and lifestyle modifications are the mainstay of treatment of LPRD. PPIs act by irreversibly inactivating $H^+ K^+$ ATPase in parietal cells of stomach. They include pantoprazole, rabeprazole, omeprazole, esomeprazole and lansoprazole. Domperidone is a prokinetic agent that acts on peripheral dopamine (D2) receptors, thereby increase the tone of lower esophageal sphincter and rate of gastric emptying.

There is a lack of studies for evaluating the efficiency of the combination of PPIs with other medications like antacids and prokinetics. In this study, we would like to compare the safety and efficacy of Rabeprazole and Domperidone combination versus Rabeprazole monotherapy in the treatment of LPRD.

II. Methodology

This randomized, open label study was conducted in Southern Railway Headquarters Hospital, Chennai, with participant allocation by Computer-generated random number sequence (randomization.org). A sample size of 54 was calculated. Clearence from ethics committee was obtained for the study.

Patients with reflux symptom index(RSI) more than 13 and reflux finding score(RFS) more than 7, with age between 18 and 80 years of either gender who gave written informed consent and followed up for 4 weeks were included in the study. Patients who were on medications for any chronic illness and pregnant women, were excluded from the study.

Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) (determined by fiber optic laryngoscopy) were the tools of assessment used. RSI was assessed by a questionnaire with 9 symptoms graded as 0-5 on the severity of scale and score more than 13 is considered as significant (Table 1).[9] It is recorded before and after 4 weeks of therapy. RFS was assessed by endoscopic grading of laryngeal signs. The total score ranged from 0-26 and score more than 7 was considered as significant (Table 2).[9] It was recorded before and after 4 weeks therapy.

Patients with LPRD were randomized into two groups A and B. The patients in group A were treated with a single capsule containing Rabeprazole 20 mg + Domperidone 30mg sustained release formulation once daily, 1 hour before breakfast for 4 weeks. The patients in group B were treated with a single tablet containing Rabeprazole 20 mg once daily 1 hour before breakfast for 4 weeks. Follow-up visits were done at 4 weeks (visit 2) after administering the study drug. A deviation of ±2 days for follow-up was accepted. All the patients included in the study were re-evaluated for Reflux Symptom Index and Reflux Finding Score at the end of 4 weeks.

Table 1: Reflux Symptom Index (RSI)[9]

1.	Hoarseness or problem with your voice	0	1	2	3	4	5
2.	Clearing of your throat	0	1	2	3	4	5
3.	Excess throat mucus or postnasal drip	0	1	2	3	4	5
4.	Difficulty in 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.	Sensation 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

Table 2 Reflux Finding Score (RFS)[9]

Sl no	Finding	Score
1.	Subglottic edema	2= present 0= absent
2.	Ventricular obliteration	2=partial 4=complete
3.	Erythema/hyperemia	2=arytenoids only 4=diffuse

4.	Vocal cord edema	1=mild 2=moderate 3=severe 4=polypoid
5.	Diffuse laryngeal edema	1=mild 2=moderate 3=severe 4=obstructing
6.	Posterior commissure hypertrophy	1=mild 2=moderate 3=severe 4=obstructing
7.	Granuloma/granulation	2= present 0= absent
8.	Thick endolaryngeal mucus or others	2= present 0= absent

III. Results:

Total number of patients included in our study were 54 and the mean age was 40.37 years. In the present study the majority of the patients were in the age group of 30-49 years (n= 34) followed by < 30 years (n= 10) (Figure1). In group A (Rabeprazole + Domperidone) the mean age was 43.07 years and in group B (Rabeprazole monotherapy) it was 37.67 years. In our study overall there were 53.7% (n= 29) males and 46.3% (n= 25) females. In group A 55.56% (n= 15) were males and 44.44% (n= 12) were females and in group B 51.85% (n= 14) were males and 48.15% (n= 13) were females(Figure 2).

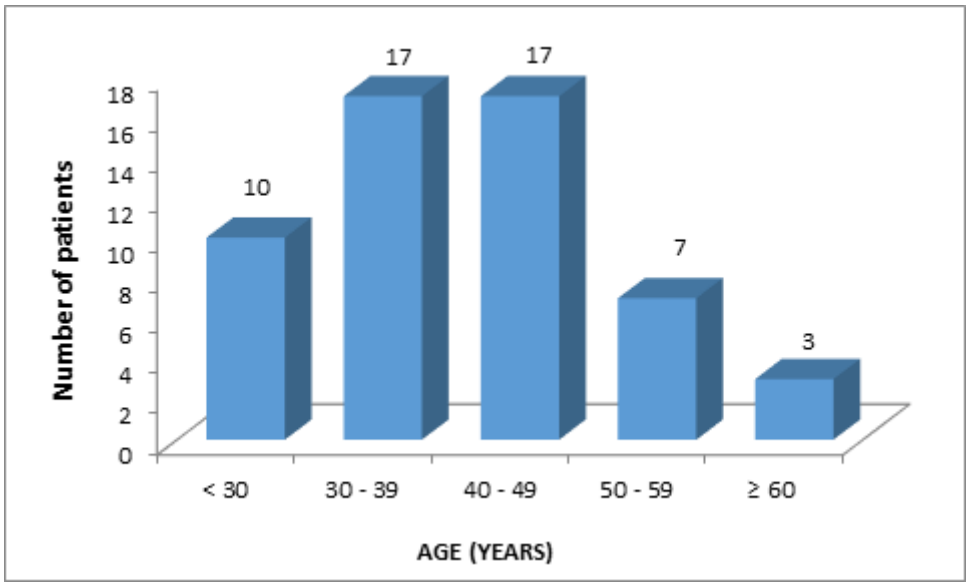

Figure 1: Age distribution of patients.

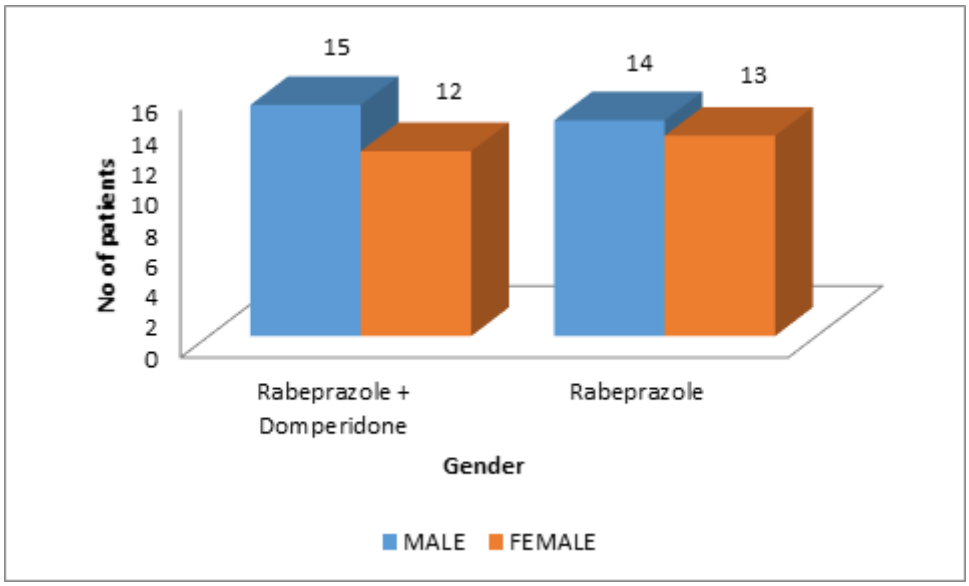

Figure 2: Gender wise distribution of patients in the study population.

Percentage distribution of symptoms

Foreign body sensation in the throat, heartburn, and frequent clearing of the throat were the most common symptoms in the present study. Other common symptoms were cough after eating or after lying down, excess throat mucus, and difficulty in swallowing food, liquid, or pills (Table 3).

Table 3: Distribution of symptoms in patients in the study population.

No	Symptoms	Number of patients in Group A	Percentage (%)	Number of patients in Group B	Percentage (%)
1.	Hoarseness or problem with your voice	12	44.4	3	11.1
2.	Clearing of your throat	26	96.3	27	100
3.	Excess throat mucus or postnasal drip	23	85.18	24	88.89
4.	Difficulty in swallowing food, liquids or pills	25	92.6	26	96.3
5.	Coughing after you ate or after lying down	25	92.6	25	92.6
6.	Breathing difficulties or choking episodes	25	92.6	22	81.14
7.	Troublesome or annoying cough	3	11.1	4	14.8
8.	Sensation of something sticking in your throat or lump in your throat	27	100	27	100
9.	Heartburn, chest pain, indigestion or stomach acid coming up.	27	100	27	100

Percentage distribution of signs

In the present study, the most common signs were erythema and posterior commissure hypertrophy followed by ventricular obliteration, endolaryngeal thick mucus, and vocal cord edema (Table 4).

Table 4: Distribution of laryngeal signs in patients in the study population

No	Reflux finding score	Number of patients in Group A	Percentage (%)	Number of patients in Group B	Percentage (%)
1.	Subglottic edema	0	0	0	0
2.	Ventricular obliteration	26	96.29	25	92.59
3.	Erythema/hyperemia	27	100	27	100
4.	Vocal cord edema	25	92. 59	25	92.59
5.	Diffuse laryngeal edema	20	74.01	21	77.78
6.	Posterior commissure hypertrophy	26	96.29	27	100
7.	Granuloma/granulation	1	3.7	0	0
8.	Thick endolaryngeal mucus or others	8	29.63	6	22.22

Reflux Symptom Index

At baseline, the mean Reflux Symptom Index (RSI) was 15.19 and 15.11 in group A and group B respectively. After 4 weeks of therapy, the mean was 7.59 (p-value < 0.0001) and 8.26 (p-value < 0.0001) in groups A and B respectively.

Among the patients, those who received Rabeprazole and Domperidone (group A) combination therapy showed statistically significant improvement in symptoms when compared to Rabeprazole monotherapy with p-value of 0.003 (Table 5 and Figure 3).

Reflux Finding Score

At baseline, the mean Reflux Finding Score was 8.19 and 8.41 in group A and group B respectively. After 4 weeks of therapy, there was an improvement in signs in patients of both the groups with a mean of 6.56 (p-value < 0.0001) and 7.07 (p-value < 0.0001) in group A and group B respectively.

There was no statistically significant difference in RFS between Rabeprazole and Domperidone (group A) combination therapy and Rabeprazole monotherapy (group B) after 4 weeks with a p-value of 0.059 (Table 5 and Figure 4).

Table 5: Distribution of Reflux symptom index and reflux finding score in patients in the study population.

	Pretreatment mean RSI	Post-treatment mean RSI	Pretreatment mean RFS	Post-treatment mean RFS
Group A (Rabeprazole+ Domperidone)	15.19	7.59	8.19	6.56
Group B (Rabeprazole)	15.11	8.26	8.41	7.07

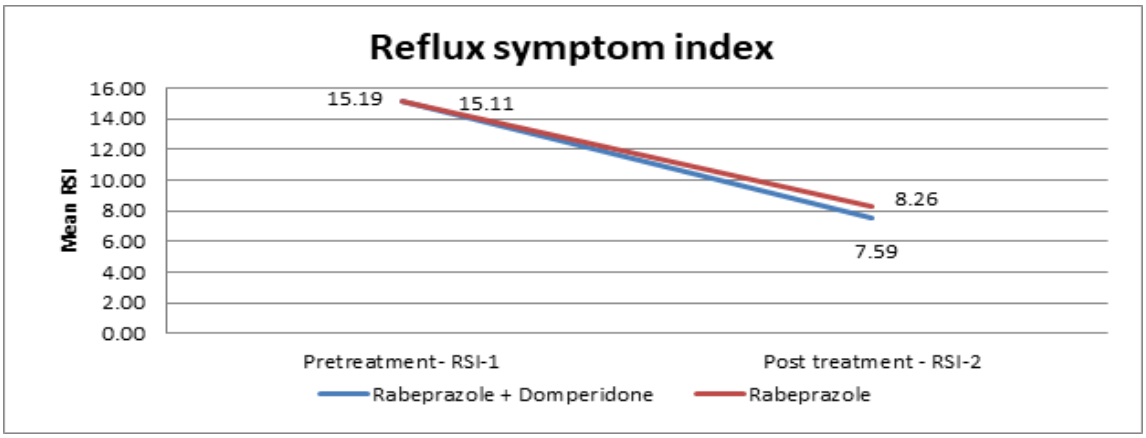

Figure 3: Comparison of RSI between group A and group B

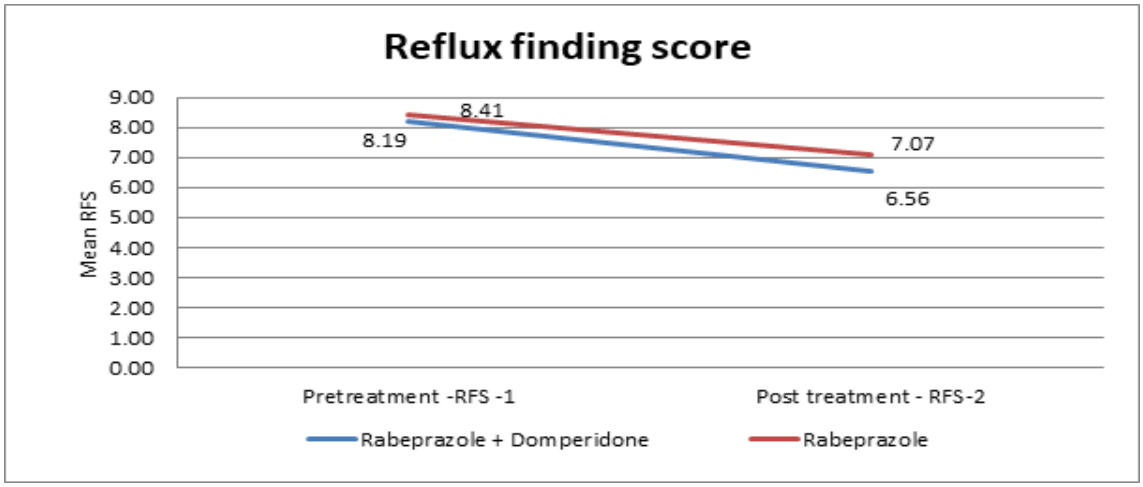

Figure 4: Comparison of RFS between group A and group B

Safety profile

In our study, 2 patients in group A reported transient diarrhea and 1 patient in group B reported mild headache, all of which were transient and self-limiting and didn't warrant any extra medical attention or discontinuation of therapy. All the patients completed the duration of therapy and tolerated the drugs well. We found that both Rabeprazole and Domperidone were safe and efficacious at clinical dosages used for the study.

IV. Discussion

Laryngopharyngeal reflux disease is a common entity encountered in otolaryngologic practice. It presents with a variety of symptoms and signs posing a difficulty in diagnosis and treatment. PPI therapy is considered as both a diagnostic and therapeutic approach for LPR. The gold standard for diagnosis of LPR and GERD is 24 hour continuous pH monitoring. [2, 10, 11]

Belafsky et al developed a validated scoring method to diagnose and assess the severity of LPRD. Reflux Symptom Index is a self-assessment questionnaire consisting of 9 symptoms and severity and is graded on a scale of 0-5 (0- no symptoms and 5- severe symptoms) in the past 1 month. Total score is 45 and score >13 is significant[82]. LPR findings commonly seen are hypertrophy of posterior commissure, laryngeal/arytenoid inflammation, and endolaryngeal mucus. [3, 4, 6] The common scale used to assess is Reflux Finding Score (RFS). Total score is 45 and score >7 is significant. Studies suggest that LPR findings differ based on the type of reflux and patient characteristics.[12] Similarly women with LPR may show lower laryngeal signs (RFS) than men.[13] The other findings include vocal cord edema, ventricular erythema, laryngeal granuloma, subglottic edema and diffuse laryngeal edema.

In the study conducted by Chun et al, there was a significant difference in post-treatment RSI between groups receiving PPI and prokinetic combination therapy and PPI monotherapy after 12 weeks. [14] Where as in another study conducted by Hunchaisri, there was no significant difference in post-treatment RSI between groups receiving PPI and prokinetic combination therapy and PPI monotherapy.[15]

Chun et al did not find statistically significant difference in post-treatment RFS between groups receiving PPI and prokinetic combination therapy and PPI monotherapy after 12 weeks.[14] In another study conducted by Hunchaisri, there was no statistically significant difference in RFS between omeprazole and domperidone group and omeprazole group after 6 weeks of therapy.[15]

In our study most common laryngeal findings were erythema/hyperemia, ventricular obliteration and diffuse laryngeal edema. Mean Reflux Finding Score were 8.19 and 8.41 in group A and group B respectively. After 4 weeks of therapy there was an improvement in signs in both the groups with a mean of 6.56 (p value < 0.0001) and 7.07 (p value < 0.0001) in group A and group B respectively.

All the patients tolerated the drugs well. We noted that both Rabeprazole and Domperidone were safe and efficacious in clinical dosages used for the study. Overall we observed that Rabeprazole with Domperidone will be better choice for improvement in symptoms of LPR and both the drugs are efficacious and tolerated well by the patients.

Further long term multi-centered double blind studies involving larger population are required to support our findings.

V. Conclusion

Rabeprazole with Domperidone combination therapy is better in improving symptoms related to laryngopharyngeal reflux disease as compared to Rabeprazole monotherapy. There was no statistically significant difference in laryngeal signs between the two therapies, although there was significant reduction from baseline in both the groups. Rabeprazole and Domperidone are well tolerated, safe and efficacious in treating LPRD.

References:

[1]. Lechien JR, Akst LM, Hamdan AL, Schindler A, Karkos PD, Barillari MR, Calvo-Henriquez C, Crevier-Buchman L, Finck C, Eun YG, Saussez S. Evaluation and management of laryngopharyngeal reflux disease: state of the art review. Otolaryngology–Head and Neck Surgery. 2019 May;160(5):762-82.

[2]. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24- hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. The Laryngoscope. 1991 Apr;101:1-78.

[3]. Habermann W, Schmid C, Neumann K, DeVaney T, Hammer HF. Reflux symptom index and reflux finding score in otolaryngologic practice. Journal of voice. 2012 May 1;26(3):e123-7.

[4]. Chappity P, Kumar R, Deka RC, Chokkalingam V, Saraya A, Sikka K. Proton pump inhibitors versus solitary lifestyle modification in management of laryngopharyngeal reflux and evaluating who is at risk: scenario in a developing country. Clinical Medicine Insights: Ear, Nose and Throat. 2014 Jan;7:CMENT-S13799.

[5]. Dore MP, Pedroni A, Pes GM, Maragkoudakis E, Tadeu V, Pirina P, Realdi G, Delitala G, Malaty HM. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. Digestive diseases and sciences. 2007 Feb 1;52(2):463-8.

[6]. Lee YS, Choi SH, Son YI, Park YH, Kim SY, Nam SY. Prospective, observational study using rabeprazole in 455 patients with laryngopharyngeal reflux disease. European archives of oto-rhino-laryngology. 2011 Jun 1;268(6):863-9.

[7]. Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngology—Head and Neck Surgery. 2000 Oct;123(4):385-8.
[8]. El–Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clinical Gastroenterology and Hepatology. 2007 Jan 1;5(1):17-26.
[9]. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). Journal of voice. 2002 Jun 1;16(2):274-7.
[10]. Zalzal GH, Tran LP. Pediatric gastroesophageal reflux and laryngopharyngeal reflux. Otolaryngologic Clinics of North America. 2000 Feb 1;33(1):151-61.
[11]. Postma GN. Ambulatory pH monitoring methodology. Annals of Otology, Rhinology & Laryngology. 2000 Oct;109(10_suppl):10-4.
[12]. Lee YC, Kwon OE, Park JM, Eun YG. Do laryngoscopic findings reflect the characteristics of reflux in patients with laryngopharyngeal reflux?. Clinical Otolaryngology. 2018 Feb;43(1):137-43.
[13]. Gao CK, Li YF, Wang L, Han XY, Wu T, Zeng FF, Li XP. Different cutoffs of the reflux finding score for diagnosing laryngopharyngeal reflux disease should be used for different genders. Acta Oto-Laryngologica. 2018 Sep 2;138(9):848-54.
[14]. Chun BJ, Lee DS. The effect of itopride combined with lansoprazole in patients with laryngopharyngeal reflux disease. European Archives of Oto-Rhino-Laryngology. 2013 Mar 1;270(4):1385-90.
[15]. Hunchaisri N. Treatment of laryngopharyngeal reflux: a comparison between domperidone plus omeprazole and omeprazole alone. Journal of the Medical Association of Thailand. 2012 Jan 20;95(1):73.

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