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LARYNGOLOGY

# The effect of itopride combined with lansoprazole in patients with laryngopharyngeal reflux disease

**Byung-Joon Chun · Dong-Soo Lee**

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**Abstract** The objective of this study is to determine the efficacy of adding a prokinetic agent to proton pump inhibitors (PPI) for the treatment of laryngopharyngeal reflux (LPR) disease. A prospective, randomized open trial comparing lansoprazole plus itopride to lansoprazole single therapy was performed for 12 weeks. Sixty-four patients with a reflux finding score (RFS) >7 and a reflux symptom index (RSI) >13 were enrolled and received either lansoprazole 30 mg once daily with itopride 50 mg three times daily or lansoprazole 30 mg once daily for 12 weeks. RSI and RFS were completed at baseline, after 6 weeks, and after 12 weeks. During the treatment period, RSI and RFS were significantly improved compared with the pretreatment scores in both study groups. Reductions of total RSI and globus symptom were significantly higher in the lansoprazole plus itopride group compared to the lansoprazole group. In the RFS, however, there were no significant differences between the two groups. In conclusion, itopride in addition to PPI did not show any superior RFS improvement compared to PPI single therapy, but was helpful in speeding up relief of reflux symptoms in LPR patients. Thus, itopride may be considered as the secondary additive agent in the PPI treatment of LPR patients.

B.-J. Chun
Department of Otolaryngology-Head and Neck Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea
e-mail: bj1000@catholic.ac.kr

D.-S. Lee (✉)
Department of Gastroenterology, College of Medicine, The Catholic University of Korea, Seoul, Korea
e-mail: cmcdj9502@catholic.ac.kr

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## Introduction

Gastroesophageal reflux disease (GERD) is a chronic symptom of mucosal damage caused by gastric acid coming up from the stomach into the esophagus [1]. GERD is usually caused by changes in the barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter. Many patients with GERD present to their gastroenterologist or primary care physician with the typical symptoms of heartburn and regurgitation. However, between 5 and 10 % of patients presenting to otolaryngologists have atypical symptoms attributed to reflux [2].

Laryngo-pharyngeal reflux (LPR) has been suggested as terms for reflux laryngitis. Although heartburn is a primary symptom among people with GERD, heartburn is present in fewer than 50 % of LPR cases [3]. The symptoms associated with LPR are hoarseness, postnasal drip, sore throat, difficulty swallowing, chronic cough, globus pharyngis and chronic throat clearing. LPR has had a significantly increasing impact on otolaryngologist office visits in the last decade [4].

The generally recommended treatment in patients with LPR is an empirical trial of proton pump inhibitors (PPIs). PPIs are considered the mainstay of medical treatment; a 3-month trial is a cost-effective approach to initial assessment and management [5]. But, the effect of the combination of PPIs and prokinetic agents for the treatment of LPR is not clear. Many authors reported that further study is needed to identify the patients with LPR who may require higher doses of PPIs or alternative treatments such as prokinetics or alginate [6].

For these reasons, we designed the study to evaluate the efficacy of using itopride as a prokinetic agent in addition to lansoprazole as a PPI in the treatment of LPR.

## Materials and methods

### Study design

A randomized, prospective open trial was performed to evaluate the efficacy of itopride as a prokinetic agent in addition to lansoprazoleas as a PPI in the treatment of LPR by evaluating change in the clinical symptoms and laryngeal findings before and after treatment.

The study was approved by the Catholic University Daejeon St. Mary's Hospital Institutional Review Board.

### Participants

Between November 2010 and May 2012, we studied 64 consecutive patients who had LPR in the Department of Otolaryngology-Head and Neck Surgery of Daejeon St. Mary's Hospital. The mean age of the subjects was 51.70 ± 12.23 (range 21–74 years), and the ratio of males to females was 54:56. The patients had non-specific laryngeal and respiratory symptoms such as chronic cough, dysphagia, throat clearing, globus sensation, hoarseness, sore throat, and heartburn within the previous month. All subjects underwent fiberoptic laryngoscopy by one otolaryngologist and the laryngoscopy had to reveal mucosal abnormalities consistent with LPR reflected by a reflux finding score (RFS) >7 [7]. In addition, the reflux symptom index (RSI), a self-administered nine-item outcome instrument for the diagnosis of LPR, had to exceed the value of 13 for inclusion. [8].

Exclusion criteria included: (1) age younger than 18 years; (2) history of PPI treatment within 1 month; (3) previously diagnosis of GERD or GERD-related complications such as Barrett's esophagus, esophageal stricture, esophageal ulcer; (4) history of gastro-intestinal(GI) surgery; (5) high risks of GI bleeding, mechanical obstruction, perforation; (6) allergy to PPI or prokinetics; (7) current systemic steroid therapy; (8) pregnancy or breast feeding; (9) diagnosis of vocal cord paralysis; (10) presence of laryngeal neoplasm requiring biopsy for diagnosis.

### Fiberoptic laryngoscopic examinations

Using fiberoptic laryngoscopy (Olympus, ENF type P3, Japan), one otolaryngologist examined the whole larynx including the mucosal status and the presence of vocal fold diseases. Every laryngoscopic examination was performed before patients' self symptom assessment. The presence of laryngopharyngeal reflux (LPR) was examined using the RFS. The RFS is an eight-item clinical severity scale based on findings obtained during fiberoptic laryngoscopy. The eight items are subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and thick endolaryngeal mucus. The scale ranges from 0 (no abnormality) to a maximum of 26 (worst score possible). Patients with RFS scores of >7 were considered to have LPR [7] (Fig. 1).

### Symptom assessment

Patients completed a self-administered nine-item RSI for the assessment of LPR symptoms. The scale for each

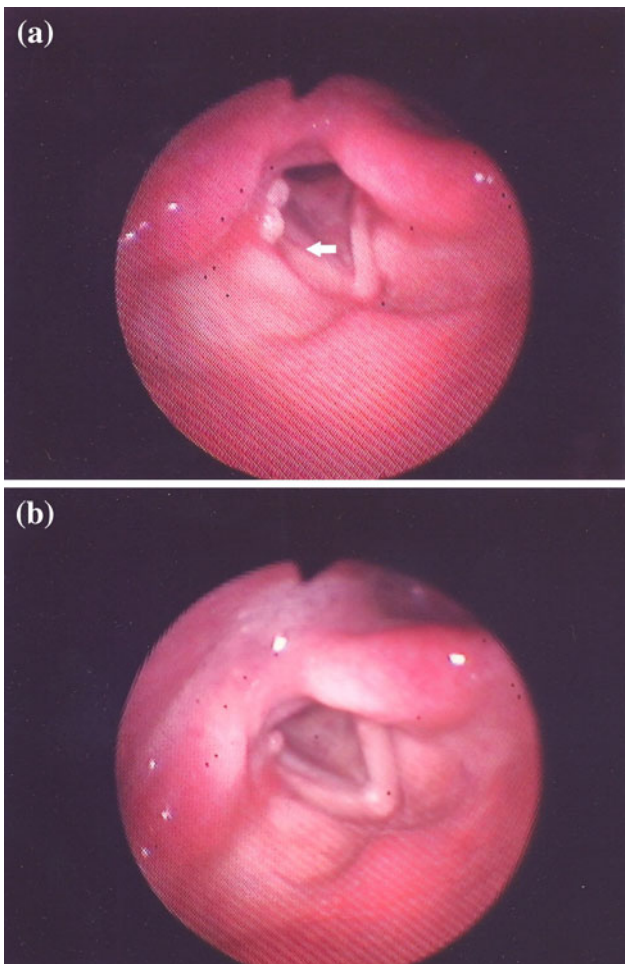


**Fig. 1** Fiberoptic laryngoscopic findings of LPR patients. **a** The fiberoptic laryngoscopic finding shows a larynx with granuloma based on the medial surfaces of left posterior arytenoid before the treatment. A pseudosulcus is identified (*white arrow*), representing subglottic edema associated with laryngopharyngeal reflux. **b** 12 weeks after the treatment, the laryngoscopic view shows that the size of granuloma was much decreased compared to the pre-treatment state

individual item ranges from 0 (no problem) to 5 (severe problem), with a maximum total score of 45 [8].

### Participant follow-up

Patients passing all inclusion and exclusion criteria were then sequentially divided randomly into two groups. The combined group received lansoprazole (30 mg once daily) before a meal and itopride 50 mg three times per day. The single group received lansoprazole 30 mg once daily before breakfast. All patients were advised on lifestyle modifications for LPR. The RFS was re-administered 6 and 12 weeks after the start of treatment by the same otolaryngologist by laryngoscopy and each patient filled in the RSI questionnaire on these two follow-up visits.

### Statistical analysis

Statistical analyses were performed using SPSS software (ver. 18.0 for Windows; SPSS, Chicago, IL, USA). For the calculation of sample size, we assumed that a typical LPR associated subscore would improve by at least one point in 65 % of the combined group and in 30 % of the single group. For comparison of those two proportions in independent samples, a sample size of 32 patients per treatment group was calculated (two-tailed $z$ test with alpha = 0.05, power = 80 %, and accounting for a 10 % drop-out rate). The baseline characteristics of both groups were compared using the Mann–Whitney $U$ test for continuous variables and the $\chi^2$ test for categorical variables. Treatment effects after 6 and 12 weeks were tested using the Wilcoxon signed-rank test. Differences in mean changes between the combined group and single group were tested using the Mann–Whitney $U$ test. A $P$ value of $<0.05$ was considered statistically significant.

## Results

Sixty-one patients completed the study. 29 patients received lansoprazole with itopride and 32 patients received lansoprazole only. One patient was lost to follow-up, and two patients were excluded due to a potential side effect (abdominal discomfort). No serious adverse events occurred in either study group except abdominal discomfort. There were no significant differences in baseline characteristics between the two groups (Table 1).

The total RSI and RFS were significantly reduced in both study groups after a treatment period of 6 weeks (Table 2). The change in total RSI score for the combined group between the baseline and second visit was higher than that of the single group. Symptoms with a statistically significant stronger change after 6 weeks for the combined group than the single group were excess mucus, troublesome cough, and globus symptom. There was no significant difference in RFS after 6 weeks of treatment between the two groups.

**Table 1** Baseline characteristics and group differences ($P$ value)

| Variable | Single group (PPI only) | Combined group (PPI + Itopride) | $P$ value* |
|---|---|---|---|
| Number of patients | 32 | 29 | |
| Age (years) | 52.15 ± 13.08 | 51.20 ± 11.44 | NS |
| Sex: male | 50 % | 48.3 % | NS |
| Smoking | 21.9 % | 31.0 % | NS |
| Alcohol | 28.1 % | 27.6 % | NS |
| Reflux symptom index (RSI) before therapy | 20.71 ± 6.47 | 22.20 ± 6.62 | NS |
| Reflux finding score (RFS) before therapy | 14.12 ± 3.65 | 14.34 ± 3.47 | NS |

* $P$ value = $\chi^2$ test or Mann–Whitney $U$ test

At the final visit, patients of both study groups were shown statistically significant improvement of total scores in RSI and RFS (Table 3). The total RSI difference was significantly higher in the combined group. The symptom with a significant stronger change in the combined group than in the single group was globus symptom. In the comparison of the total RFS reduction between the two study groups, there was no statistically significance between two groups.

## Discussions

Laryngopharyngeal reflux had a relatively high incidence for otolaryngologist. Approximately 10–30 % of patients visiting the otolaryngologist, and more than half of all patients with voice and laryngeal problems, have conditions related to LPR [8, 9].

The efficacy of proton pump inhibitors for the treatment of LPR has been well recognized in many studies. The first study to use PPI was by Kamel who used omeprazole [3]. They reported that laryngeal symptoms and findings in LPR patients were improved after 6–24 weeks of omeprazole treatment. In another report, twice-daily PPI for 2–4 months has been recommended in patients with signs and symptoms of LPR [10, 11]. However, few studies were reported with regard to the combined treatment of LPR with PPI and the prokinetic agent.

The pathophysiology of GERD is multifactorial and involves several well-known mechanisms such as failure of the antireflux barrier, impaired esophageal clearance, and defective esophageal mucosal resistance. Among the

**Table 2** Treatment effects after 6 weeks

| Variables | Baseline vs. second visit | | | | | |
|---|---|---|---|---|---|---|
| | PPI only ($n = 32$) | | PPI + itopride ($n = 29$) | | PPI vs. PPI + itopride | |
| | Change | $P$ value* | Change | $P$ value* | Difference | $P$ value† |
| RSI | | | | | | |
| Total | 8.84 ± 5.66 | $P < 0.001$ | 12.51 ± 5.78 | $P < 0.001$ | −3.67 ± 1.46 | $P < 0.05$ |
| Hoarseness | 0.78 ± 0.83 | $P < 0.001$ | 0.82 ± 0.92 | $P < 0.001$ | −0.04 ± 0.22 | NS |
| Clearing throat | 0.78 ± 0.94 | $P < 0.001$ | 1.31 ± 1.51 | $P < 0.001$ | −0.53 ± 0.31 | NS |
| Excess mucus | 0.84 ± 0.98 | $P < 0.001$ | 1.48 ± 1.08 | $P < 0.001$ | −0.64 ± 0.26 | $P < 0.05$ |
| Swallowing difficulty | 1.43 ± 1.24 | $P < 0.001$ | 1.55 ± 1.02 | $P < 0.001$ | −0.11 ± 0.29 | NS |
| Coughing after meal | 1.03 ± 1.12 | $P < 0.001$ | 1.48 ± 1.02 | $P < 0.001$ | −0.45 ± 0.27 | NS |
| Breathing difficulty | 1.46 ± 1.45 | $P < 0.001$ | 1.31 ± 1.10 | $P < 0.001$ | 0.15 ± 0.33 | NS |
| Troublesome cough | 0.96 ± 1.23 | $P < 0.001$ | 1.58 ± 1.23 | $P < 0.001$ | −0.62 ± 0.31 | $P < 0.05$ |
| Globus symptom | 0.65 ± 1.12 | $P < 0.01$ | 1.65 ± 1.14 | $P < 0.001$ | −0.99 ± 0.29 | $P < 0.05$ |
| Heartburn | 0.90 ± 0.99 | $P < 0.001$ | 1.31 ± 1.10 | $P < 0.001$ | −0.40 ± 0.26 | NS |
| RFS | | | | | | |
| Total | 4.00 ± 3.11 | $P < 0.001$ | 4.48 ± 3.23 | $P < 0.001$ | −0.48 ± 0.81 | NS |
| Subglottic edema | 0.37 ± 0.94 | $P < 0.05$ | 0.55 ± 1.05 | $P < 0.05$ | −0.17 ± 0.25 | NS |
| Ventricular obliteration | 0.93 ± 1.13 | $P < 0.001$ | 0.55 ± 1.05 | $P < 0.05$ | 0.38 ± 0.28 | NS |
| Erythema | 0.87 ± 1.00 | $P < 0.001$ | 0.48 ± 0.87 | $P < 0.01$ | 0.39 ± 0.24 | NS |
| Vocal fold edema | 0.43 ± 0.80 | $P < 0.01$ | 0.68 ± 0.66 | $P < 0.001$ | −0.25 ± 0.18 | NS |
| Diffuse laryngeal edema | 0.59 ± 0.79 | $P < 0.01$ | 1.06 ± 1.13 | $P < 0.001$ | −0.47 ± 0.24 | NS |
| Posterior commissure hypertrophy | 0.21 ± 0.60 | 0.052 | 0.44 ± 0.68 | $P < 0.05$ | −0.23 ± 0.16 | NS |
| Granulation tissue | 0.18 ± 0.59 | 0.083 | 0.34 ± 0.76 | $P < 0.05$ | −0.15 ± 0.17 | NS |
| Thick endolaryngeal mucus | 0.37 ± 0.94 | $P < 0.05$ | 0.34 ± 0.93 | 0.059 | 0.03 ± 0.24 | NS |

Data are given as mean differences ± standard error of the mean (SEM)

* $P$ values for mean change from pretreatment baseline within groups using Wilcoxon signed-rank test

† $P$ values for difference in mean change between groups using Mann–Whitney $U$ test

dysfunctions of the antireflux barrier, transient lower esophageal sphincter (LES) relaxations comprise the major mechanism underlying gastro-esophageal reflux events in a majority of GERD patients [12].

The prokinetic agents increase acetylcholine concentrations by antagonizing the M1 receptor which inhibits acetylcholine release, or by inhibiting the enzyme acetylcholinesterase, which metabolizes acetylcholine. Higher acetylcholine levels increase gastrointestinal peristalsis and further increase pressure on the lower esophageal sphincter, thereby stimulating gastrointestinal motility, accelerating gastric emptying [13, 14]. In one report, concomitant use of prokinetics resulted in significant increases of the maximum plasma concentrations (C(max)) and the time-plasma concentration curve (AUC) of PPI, and co-administration of prokinetics could have some favorable effect in PPIs-based therapy [15]. Therefore, prokinetic agents have been developed and generally used in the treatment of the acid reflux disease.

Itopride is a novel prokinetic agent acting both as a dopamine D2 receptor antagonist and as an acetylcholine esterase inhibitor. It accelerates gastric emptying, improves gastric tension and sensitivity, and has an anti-emetic action. It was also identified to have equivalent efficacy with cisapride in functional dyspepsia [16]. In addition, itopride did not demonstrate any inhibitory effect on five specific cytochrome P450-mediated reactions in human liver microsomes, and itopride is unlikely to cause clinically significant pharmacokinetic drug interactions [17].

In this study, we used PPI therapy of lansoprazole at 30 mg once daily in both groups, and added itopride as a prokinetic agent to evaluate the benefit of adding a prokinetic agent in the treatment of LPR patients. There was a statistically significant difference between the two groups in the total RSI, excess mucus, troublesome cough, and globus symptom (Table 2). In the laryngeal findings (RFS), the itopride group improved slightly compared to the single group, but there was no statistical significance. After 12 weeks of treatment, the difference for the total RSI between the two groups was statistically bigger compared to 6 weeks, but the difference of total RFS between the two groups was not statistically significant. At the end period of

**Table 3** Treatment effects between baseline and third visit

| Variables | Baseline vs. third visit | | | | | |
|---|---|---|---|---|---|---|
| | PPI only ($n = 32$) | | PPI + itopride ($n = 29$) | | PPI vs. PPI + itopride | |
| | Change | $P$ value* | Change | $P$ value* | Difference | $P$ value† |
| RSI | | | | | | |
| Total | 12.40 ± 5.69 | $P < 0.001$ | 15.10 ± 6.38 | $P < 0.001$ | −2.69 ± 1.54 | $P < 0.05$ |
| Hoarseness | 1.21 ± 1.03 | $P < 0.001$ | 1.41 ± 1.11 | $P < 0.001$ | −0.19 ± 0.27 | NS |
| Clearing throat | 1.62 ± 1.15 | $P < 0.001$ | 1.93 ± 1.60 | $P < 0.001$ | −0.30 ± 0.35 | NS |
| Excess mucus | 1.31 ± 1.22 | $P < 0.001$ | 1.79 ± 1.31 | $P < 0.001$ | −0.48 ± 0.32 | NS |
| Swallowing difficulty | 1.75 ± 1.04 | $P < 0.001$ | 1.68 ± 1.16 | $P < 0.001$ | 0.06 ± 0.28 | NS |
| Coughing after meal | 1.31 ± 1.33 | $P < 0.001$ | 1.75 ± 1.15 | $P < 0.001$ | −0.44 ± 0.32 | NS |
| Breathing difficulty | 1.68 ± 1.46 | $P < 0.001$ | 1.51 ± 1.24 | $P < 0.001$ | 0.17 ± 0.35 | NS |
| Troublesome cough | 1.21 ± 1.28 | $P < 0.001$ | 1.62 ± 1.32 | $P < 0.001$ | −0.40 ± 0.33 | NS |
| Globus symptom | 1.15 ± 1.39 | $P < 0.001$ | 1.79 ± 1.23 | $P < 0.001$ | *−0.63* ± 0.33 | $P < 0.05$ |
| Heartburn | 1.15 ± 1.24 | $P < 0.001$ | 1.58 ± 1.23 | $P < 0.001$ | −0.42 ± 0.31 | NS |
| RFS | | | | | | |
| Total | 5.09 ± 3.15 | $P < 0.001$ | 5.41 ± 3.19 | $P < 0.001$ | −0.32 ± 0.81 | NS |
| Subglottic edema | 0.68 ± 1.09 | $P < 0.01$ | 0.68 ± 1.10 | $P < 0.01$ | 0.00 ± 0.28 | NS |
| Ventricular obliteration | 1.25 ± 1.31 | $P < 0.001$ | 0.75 ± 1.24 | $P < 0.01$ | 0.49 ± 0.32 | NS |
| Erythema | 0.93 ± 1.24 | $P < 0.001$ | 0.68 ± 0.96 | $P < 0.01$ | 0.24 ± 0.28 | NS |
| Vocal fold edema | 0.53 ± 0.94 | $P < 0.01$ | 0.75 ± 0.87 | $P < 0.001$ | −0.22 ± 0.23 | NS |
| Diffuse laryngeal edema | 0.71 ± 0.99 | $P < 0.001$ | 1.17 ± 1.19 | $P < 0.001$ | −0.45 ± 0.28 | NS |
| Posterior commissure hypertrophy | 0.43 ± 0.84 | $P < 0.01$ | 0.72 ± 0.84 | $P < 0.001$ | −0.28 ± 0.21 | NS |
| Granulation tissue | 0.09 ± 0.96 | NS | 0.34 ± 0.81 | $P < 0.05$ | −0.25 ± 0.22 | NS |
| Thick endolaryngeal mucus | 0.43 ± 0.98 | $P < 0.05$ | 0.27 ± 1.03 | NS | 0.16 ± 0.25 | NS |

Data are given as mean differences ± standard error of the mean (SEM)

* $P$ values for mean change from pretreatment baseline within groups using Wilcoxon signed rank test

† $P$ values for difference in mean change between groups using Mann–Whitney $U$ test

the treatment, the total change of RSI in the two groups from basal 20 and 22 to 6 and 7, respectively, gives a normalization of RSI (<14) in both groups, whereas the change of RFS from 14 to 9 in both groups does not decrease RFS below the limit score of 7. These results did not show that itopride increased the efficacy of PPI therapy effectively in the treatment of LPR, but it is helpful to relieve reflux symptom in a shorter time than PPI single therapy in the LPR patients.

**Conflict of interest** None.

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