Comparison between Omeprazole Plus Baclofen and Omeprazole Plus Placebo in the Treatment of Laryngopharyngeal Reflux

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Background: *At present, baclofen was generally used for treatment of refractory gastroesophageal reflux disease (GERD). Better improvement in the symptoms of GERD, such as heart burn and globus sensation, was demonstrated by administration of baclofen compared to proton-pump inhibitor treatment alone. There was no study about baclofen for the treatment of laryngopharyngeal reflux (LPR) in the English literature. This study was conducted to evaluate the usefulness of baclofen in LPR treatment.*

Objective: *To evaluate the efficacy of baclofen in the treatment of Laryngopharyngeal reflux (LPR).*

Material and Method: *This study was performed in the outpatient clinic of Otorhinolaryngology, Head and Neck surgery department, HRH Princess Maha Chakri Sirindhorn Medical center (MSMC), Srinakharinwirot University. Patients who were diagnosed with LPR were divided into 2 groups by randomized, double blind technique. The study group received omeprazole and baclofen for 1 month. The control group received omeprazole and placebo drug in the same doses. Data were recorded as general characteristics, reflux symptom index (RSI), and reflux finding score (RFS) before and after treatment. RSI and RFS were used for evaluation at the end of the study. Qualitative variables were compared with Fisher's exact test, whereas quantitative variables were done with Wilcoxon nonparametric test. Drug adverse effects were also recorded.*

Result: *At the end of the study, 30 patients were collected of which 15 patients were in the study group and 15 patients were in the control group. Before treatment, there were no statistical significant differences in age, BMI, RSI and RFS between both groups. After treatment, no significant difference between two groups were detected in RSI at 1 week and 1 month (p-value = 0.598 and 0.552, respectively) and in RFS at 1 month (p-value = 0.979). There were more adverse effects in the study group such as drowsiness, dizziness, nausea and vomiting.*

Conclusion: *Addition of baclofen to omeprazole in the treatment of LPR patients did not show better results than omeprazole alone.*

Keywords: *Laryngopharyngeal reflux (LPR), Baclofen, Omeprazole, Reflux symptom index (RSI), Reflux findings score (RFS)*

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Gastroesophageal reflux disease (GERD) is generally divided into 2 groups. The group that has reflux from stomach into esophagus is called esophageal reflux disease and the other group that has reflux into area beyond the esophagus is called extraesophageal reflux disease especially laryngopharyngeal reflux (LPR). The clinical manifestations of GERD vary according to the affected sites by the refluxates[1]. The symptoms of laryngopharyngeal reflux are the results of irritation to a patient's larynx and pharynx. The common symptoms included chronic cough (97%), a lot of secretion in the throat (98%), hoarseness (95%) and lump in throat (95%)[2]. Laryngeal examination usually showed inflamed mucosa and sometimes vocal cord nodules may be found[1]. Additionally, approximately 60% of patients with esophageal reflux also exhibited laryngopharyngeal reflux symptoms[3,4]. The mechanisms of reflux remained not completely understood and controversy. The refluxates are composed of many substances such as gastric acid, pepsin enzyme, bile slats, and pancreatic proteolytic enzymes. Although acid reflux can be treated with proton pump inhibitor[5], the other components still cannot be treated effectively[6].

Nowadays, Reflux Symptom Index (RSI)[7]

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Table 1. Reflux symptom Index (RSI)

Within the last month, how did the following problems affect you? Circle the appropriate response.	0 = no problem 5 = severe problem					
1) Hoarseness or a problem with your voice	0	1	2	3	4	5
2) Clearing your throat	0	1	2	3	4	5
3) Excess throat mucus or post nasal drip	0	1	2	3	4	5
4) Difficult swallowing food, liquid, 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

* Belafsky[7]

score (Table 1) and Reflux Finding Score (RFS)[8] (Table 2) created by Belafsky are useful tools in diagnosis and follow-up LPR patients. These scoring systems have been tested for their validity and reliability[7,8]. Patients with RSI score more than 13 points and RFS more than 7 points are considered to be LPR. The patients who do not relieve symptoms are needed for further evaluation by the special tests especially 24-hour dual channel pH probe monitoring and/or esophagogastroduodenoscopy[9].

The treatments of LPR included life-style modification, medication and surgery in some circumstance. Proton pump inhibitor is the main medical treatment for both GERD and LPR but with varying success.

Baclofen, a gamma-aminobutyric acid (GABA) agonist, is the drug that is used to treat spastic disorder. It has been shown to inhibit transient lower esophageal sphincter (LES) relaxation and decreased gastrointestinal reflux at dosage 40 mg per day to maximum dosage 100 mg per day[10,11]. The dosage of 40 mg per day was demonstrated that can decrease transient LES relaxation in 60% of population in some studies[12]. In another study found improvement of GERD symptoms and esophageal reflux tested by 12-hour ambulatory pH meter[12]. Furthermore, in one research, 30 mg per day of baclofen for a month was reported to increase in pH and relieve of GERD symptoms just in a few days after start treatment and lower drug adverse effect than conventional regimen[13]. There was no study about baclofen for the treatment of laryngopharyngeal reflux (LPR) in the English literature. This study was conducted to evaluate the usefulness of baclofen in LPR treatment.

Table 2. Reflux finding score (RFS)

Subglottic edema	0 = absent 2 = present
Ventricle	2 = partial 4 = complete
Erythema/hyperemia	2 = arytenoid only 4 = diffuse
Vocal fold edema	1 = mild 2 = moderate 3 = severe 4 = polypoid
Diffuse laryngeal edema	1 = mild 2 = moderate 3 = severe 4 = obstructing
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing
Granuloma/granulation tissue	0 =absent 2 = present
Thick endolarynx mucus	0 = absent 2 = present

*Belafsky[8]

Material and Method

From September 2016 to February 2017, a prospective, double-blinded, randomized, controlled trial was performed in the patients who diagnosed as LPR and signed the written informed consent. Inclusion criteria were age 18 to 60 years, RSI >13 points and RFS >7 points, symptoms persist more than one month, and no previous medical treatment for LPR during 1 month period. Exclusion criteria were pregnancy or on breast

feeding, severe or uncontrolled medical problems (such as cardiovascular disease, kidney disease, cerebrovascular disease, hypertension, and diabetes), unaccepted drug adverse effects or allergy to Baclofen, and unwilling to continue in the study. The present study was approved by the Ethic Review Boards of the Faculty of Medicine, Srinakharinwirot University (SWUEC/F-137/2558).

Data collected

The baseline data including age, weight, height, history of allergy, history of drug used, smoking, RSI scores, and RFS were recorded. Laryngostroboscopy was used for evaluation of RFS by two specialists not known about the diagnosis of the patients. RSI scores are recorded before treatment and at 1 week and 4 weeks after treatment. The RFS is evaluated before and 4 weeks after treatment.

Study protocol

All patients were allocated into study group and control group by a block randomized design. The study group received omeprazole 20 mg and baclofen 20 mg which were taken 30 minute before meals in the morning and evening for 4 weeks. The control group received omeprazole 20 mg and placebo in the same doses. This study was designed as double blinded method. Both groups of patients, they did not know naming of a taken drug. Moreover, the examiner did not know the groups of patients. All any adverse effects occurred during the therapy were recorded. The patients not tolerated to the adverse effects were excluded from the study.

Statistical analysis

Qualitative variables were compared with Chi-square or Fisher's exact test, whereas quantitative variables were done with Student's t or Wilcoxon nonparametric test. Statistical significance was considered when $p<0.05$.

Results

At the end of the study, a total of 30 patients were collected. There were 15 patients in each group. The basic characteristics of the patients in both groups, including RSI and RFS, showed no statistical differences (Table 3).

After completing the study period, post-treatment RSI scores showed significant improvement at 1 week and 4 weeks in both groups ($p<0.001$) (Table 4). However, when compared between two groups, there were no statistical differences ($p = 0.6$ and 0.55) (Table

Table 3. Basic demographic data

	Baclofen group	Placebo group	*p*-value
Sex			0.46
Male (%)	6 (42.9)	8 (57.1)	
Female (%)	9 (56.3)	7 (43.8)	
Age (mean ± SD)	43.47±9.54	49.07±10.31	0.12
BMI (mean ± SD)	25.41±5.45	25.25±4.15	0.93
Smoking			1.00
Yes (%)	4 (50)	4 (50)	
No (%)	11 (50)	11 (50)	
Pre-RSI (mean ± SD)	21.60±6.23	23.87±5.82	0.31
Pre-RFS (mean ± SD)	12.60±2.69	12.67±2.10	0.94

RSI = reflux symptom index; RFS = reflux finding score; SD = standard deviation; BMI = body mass index

Table 4. RSI of baclofen and placebo group at 4 week after treatment

RSI	Pre-treatment	4 week	*p*-value
Baclofen	21.60±6.23	9.08±2.94*	<0.001
Placebo	23.87±5.82	8.38±2.84*	<0.001

RSI = reflux symptom index

Table 5. RSI between placebo and baclofen group at 1 week and 4 week after treatment

RSI	Baclofen	Placebo	Mean difference	95% CI	*p*-value
Pre-treatment	21.60±6.23	23.87±5.82	2.26	-2.25 to 6.78	0.31
1 week	16.17±3.97	16.93±3.29	0.76	-2.18 to 3.70	0.60
4 weeks	9.08±2.94	8.38±2.84	-0.68	-3.09 to 1.69	0.55

RSI = reflux symptom index

Table 6. RFS between placebo and baclofen group at 4 week after treatment

RFS	Baclofen	Placebo	Mean difference	95% CI	*p*-value
Pre-treatment	12.60±2.69	12.67±2.09	0.067	-1.74 to 1.87	0.94
4 weeks	6.42±3.23*	6.38±2.87*	-0.032	-2.56 to 2.50	0.98

RFS = reflux finding score, * $p<0.001$

5). The results of RFS were same as RSI. Statistical improvement of RFS was demonstrated in both groups at 4 weeks, but no significant differences between two groups ($p = 0.98$) (Table 6).

Nine patients in study group reported many adverse effects. Drowsiness (46%) was most common follow by dizziness 33%, motion sickness 33%, lump in throat 13% and dryness on month and lip 6%. No adverse effects reported in control group. Five patients were excluded from the study, 2 in the control group were lost to follow-up and 3 in the study group cannot tolerate adverse effects. There was one patient who needed hospital admission due to severe nausea and vomiting.

Discussion

After therapy, both RSI and RFS were significant improvement in both groups. Nevertheless, when comparing the results of the therapy between 2 groups, there was no significant difference. The results of the present study were contrast with the previous studies[14-16]. The contrast results may have occurred from the fact that all subjects in the previous researches were GERD patients but in the present study were LPR patients. This result may reflect the different pathophysiology between GERD and LPR. GERD has LES dysfunction while LPR has both LES and upper esophageal sphincter (UES) dysfunction. The action of baclofen may exhibit only inhibition of LES relaxation but no effect on UES function. This is because the relaxation of UES consists of two mechanisms. Firstly, the relaxation is originated by motor neuron of nucleus ambiguus. Secondly, the relaxation comes from contraction of suprahyoid muscle. When contracting, it makes anterior and superior lift of hyoid and cricoid bone[15]. Therefore, usage of baclofen can inhibit particularly in motor neuron function. That is why baclofen has no further benefit when combined with omeprazole compared to omeprazole alone in LPR treatment.

The limitations of the present study are the small number of subjects and the clinical experience from a single institution.

Conclusion

The present study demonstrated that addition of baclofen to omeprazole in the treatment of LPR patients did not show better results than omeprazole alone. Nevertheless, more sample sizes and well-designed studies are needed to verify the benefit of baclofen in LPR patients.

What is already known on this topic?

Baclofen (gamma-aminobutyric acid (GABA) receptor agonist) has effectiveness when combined with proton pump inhibitors for treatment of gastroesophageal reflux disease.

What this study adds?

The present study revealed that treatment with

baclofen in LPR patients did not have better results than placebo. Besides, there were adverse drug reactions occurred only in patients received baclofen.

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Potential conflicts of interest

None.

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การเปรียบเทียบการใช้ยาโอเมพราโซลร่วมกับยาบาโคลเฟนและโอเมพราโซลร่วมกับยาหลอกในการรักษากรดไหลย้อนมาที่คอและกล่องเสียง

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ภูมิหลัง: ปัจจุบันมีการใช้ยา Baclofen เป็นยาร่วมในการรักษาโรคกรดไหลย้อนมาที่หลอดอาหาร (GERD) พบว่าสามารถลดการเกิดอาการแสบร้อนกลางอก จุกคอ และลดความรุนแรงของอาการได้ เมื่อเทียบกับการให้ยาลดกรดเพียงอย่างเดียว เนื่องจากยังไม่มีงานวิจัยเกี่ยวกับการใช้ยา Baclofen ในการรักษาโรคกรดไหลย้อนมาที่คอและกล่องเสียง (LPR) มาก่อนจึงเป็นที่มาของการศึกษานี้ที่ต้องการทราบประโยชน์ของยา Baclofen ในการรักษาโรค LPR

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของยา Baclofen ในการรักษาผู้ป่วยกรดไหลย้อนมาที่คอและกล่องเสียง

วัสดุและวิธีการ: ทำการศึกษาที่ห้องผู้ป่วยนอกแผนกหู คอ จมูก ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ มหาวิทยาลัยศรีนครินทรวิโรฒ ผู้ป่วยที่ได้รับการวินิจฉัยเป็นกรดไหลย้อนมาที่คอและกล่องเสียง ถูกแบ่งออกเป็นสอง กลุ่มโดยการสุ่ม กลุ่มทดลองได้รับการรักษาด้วยยา Baclofen ร่วมกับ Omeprazole เป็นระยะเวลา 1 เดือน และกลุ่มควบคุมได้รับยา Omeprazole ร่วมกับยาหลอกเป็นระยะเวลาเท่ากัน มีการเก็บข้อมูลทั่วไปผู้ป่วย ได้แก่ ค่า Reflux symptom index (RSI) และค่า Reflux finding score (RFS) ทั้งก่อนและหลังการรักษา ประเมินประสิทธิภาพของยาโดยใช้ค่า RSI ก่อนและหลังการรักษาที่ 1 สัปดาห์และ 1 เดือนและค่า RFS ก่อนและหลังการรักษา 1 เดือน เปรียบเทียบกัน ผลข้างเคียงของยาในแต่ละกลุ่มจะถูกบันทึกไว้

ผลการศึกษา: เมื่อสิ้นสุดการศึกษามีผู้ป่วยทั้งหมด 30 คน แบ่งเป็นกลุ่มละ 15 คน โดยก่อนการรักษา ไม่พบความแตกต่างกันในอายุ, เพศ, BMI, ค่า RSI และค่า RFS ในสองกลุ่ม หลังการรักษาพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มสองกลุ่ม เมื่อเปรียบเทียบค่า RSI ก่อนและหลังการรักษาที่ 1 สัปดาห์และ 1 เดือน (p-value = 0.598 และ 0.552 ตามลำดับ) และค่า RFS ก่อนและหลังการรักษา 1 เดือน (p-value = 0.979) พบผลข้างเคียงในกลุ่มทดลองได้แก่ อาการง่วงนอน เวียนศีรษะ คลื่นไส้ อาเจียนมากกว่ากลุ่มควบคุม

สรุป: การให้ยา Baclofen เสริมร่วมกับ omeprazole ในการรักษาโรคกรดไหลย้อนมาที่คอและกล่องเสียงได้ผลไม่ดีไปกว่าการให้ยา omeprazole เพียงอย่างเดียว