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A new approach to vocal cord leukoplakia and evaluation of proton pump ınhibitor treatment

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Abstract

Purpose Our aim is identify a new approach to vocal cord leukoplakia treatment and detect to efficiency of proton pump inhibitors.

Study design Prospective, nonrandomized experimental clinical trial.

Methods A 'First Assessment Scale' was prepared. This scale included the lesion's and the patient's characteristics. Using this scale, 24 patients included to the study. 20 mg rabeprazole twice daily was applied to all patients. At the end of 3rd month, a 'Second Assessment Scale' was used and two groups created. In group 1, 19 patients were accepted to responsive for the therapy and received the same therapy. The group 2 was included five patients that accepted unresponsive to treatment and directed to surgery. All patients received the same treatment additionally 3 months. At the end of 6th month, the Reflux Symptom Index (RSI), the Reflux Finding Score (RFS) and the Red–Green–Blue (RGB) values evaluated and comparisons were made.

Results The RSI and RFS values were significantly decreased in all patients. The Red values were significantly decreased with treatment in group 1, but the Green and Blue values were not. In group 2, the RGB values were not showed the significant differences. In conclusion, seven patients (29,2%) showed complete lesion regression, 12 patients (50%) showed partial lesion regression and five patients (20,8%) showed no response to treatment.

Conclusions The proton pump inhibitor treatment may be beneficial for the selected patients. The scales that we prepared were useful for lesion assesment.

Keywords Vocal cord leukoplakia · Laryngopharyngeal reflux · Rabeprazole · Proton pump inhibitor · Leukoplakia · Precancerous

Introduction

Leukoplakia, which is Latin for "white plaque", is keratinised tissue over the epithelium that cannot be removed easily. Durant coined the term laryngeal leukoplakia [1, 2]. hypothesised that laryngeal leukoplakia was the precursor of laryngeal carcinoma [2]. It is now clear that leukoplakia is a precancerous lesion.

Laryngopharyngeal reflux (LFR) occurs when the gastroesophageal contents reach the larynx and pharynx, and results from early premature relaxation of the upper oesophageal sphincter. The role of LFR in the etiology of vocal cord leukoplakia is well known. Proton pump inhibitors are the most common treatment for LFR.

This study developed a new algorithm for the treatment of vocal cord leukoplakia and investigated the efficacy of rabeprazole therapy.

Materials and methods

This study was approved by Bezmialem Vakif University Clinical Research Ethics Committee on 07/12/2016. The study enrolled 24 patients who were admitted to our clinic between September 2015 and September 2016 with hoarseness or decreased voice quality who were diagnosed with vocal cord leukoplakia after video stroboscopic examination.

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Age, sex, smoking, and alcohol use were recorded for all patients.

At the first visit and after 3 and 6 months of treatment, each patient was asked to complete the reflux symptom index (RSI) form (Table 1). The reflux finding score (RFS) was calculated for each patient (Table 2). Laryngeal examinations of the patients were performed by the same physician using the same videostroboscope (Xion, Berlin, Germany). Using larynx photographs, the red–green–blue (RGB) values of eight laryngeal regions were recorded: the epiglottis, right and left piriform sinus, right and left vocal cord, right and left arytenoid, and posterior commissure. The RGB values of the regions were measured at four different points using Adobe® Photoshop® CS6 ver. 13.1.2 × 64 (Adobe Systems, San Jose, CA, USA) and the mean values were calculated.

We developed a 'First Examination Scale' (Table 3) and applied it to all patients. Patients with a score of 13 or over were deemed to be at malignancy risk and treated with the appropriate surgery and excluded from the study.

The remaining patients were treated with 20 mg rabeprazole twice a day for the first 3 months. Dietary and lifestyle changes were suggested. After 3 months, the patients were re-evaluated with videostroboscopy, the RSI and RFS were calculated and the RGB measurements repeated.

The 'Second Examination Scale' was applied at 3 months (Table 4) and patients were divided into two groups according to the regression of the lesion. On this scale, scores of 8 and below were associated with lesion regression, and the treatment was continued for 3 months in these patients (group 1, $n = 19$). Patients with a score above 8 (group 2, $n = 5$) were deemed unresponsive to treatment, and these patients were directed to surgery. Microlaryngeal surgery was performed by the same surgeon using the same method. These patients were followed for recurrence with the same proton pump inhibitor (PPI) treatment for 3 months postoperatively.

Table 2 Reflux finding score

Subglottic edema	Absent: 0
	Present: 2
Ventricular obliteration	Partial: 2
	Complete: 4
Erythema/hyperemia	Only arytenoids: 2
	Diffuse: 4
Vocal fold edema	Mild: 1
	Moderate: 2
	Severe: 3
	Polypoid: 4
Diffuse laryngeal edema	Mild: 1
	Moderate: 2
	Severe: 3
	Obstructing: 4
Posterior commissure hypertrophy	Mild: 1
	Moderate: 2
	Severe: 3
	Obstructing: 4
Granuloma/granulation tissue	Absent: 0
	Present: 2
Thick endolaryngeal mucus	Absent: 0
	Present: 2
Total score	

A score above 7 is considered positive for LPR

The measurements were compared after 6 months using SPSS ver. 24.0 (SPSS, Chicago, IL, USA). Descriptive statistics were calculated as the mean and standard deviation. Repeated one-way analysis of variance (ANOVA) was used to compare the RSI, RFS, and RGB values. Values of $p < 0.05$ were accepted as statistically significant.

Table 1 Reflux symptom index

	(0: no problem, 5: severe problem)					
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucus or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
Heartburn, chest pain, indigestion, or stomach and coming up	0	1	2	3	4	5
Total score						

A score above 13 is considered positive for LPR

Table 3 Firt examination scale

	Score
Age (years)	
< 60	0
≥ 60	+1
Sex	
Female	0
Male	+1
Smoking	
No smoking	0
0–10 pack/year	+1
10–20 pack/year	+2
> 20 pack/year	+3
Drinking alcohol	
No	0
Yes	+1
Characteristics of lesion	
Colour	
Homogenous	+1
Heterogenous	+2
Margins	
Regular	+1
Irregular	+2
Hyperemia	
Yes	+1
No	+2
Thickness	
Thin (capillary blood vessels appear)	+1
Thick (capillary blood vessels do not appear)	+2
Locations of lesion	
Posterior commissure	+1
Posterior 1/3 of vocal cord	+2
Middle 1/3 of vocal cord	+3
Anterior 1/3 of vocal cord	+4
Anterior commissure	+5
Total score	

A score above 13 is considered to positive for malignancy. Therefore, the patients that have 13 and more scores excluded from the study and they directed to surgery

Table 4 Second examination scale

	Score
Characteristics of lesion	
Colour	
Homogenous	+1
Heterogenous	+2
Margins	
Regular	+1
Irregular	+2
Hyperemia	
Yes	+1
No	+2
Thickness	
Thin (capillary blood vessels appear)	+1
Thick (capillary blood vessels do not appear)	+2
Location of lesion	
Posterior commissure	+1
Posterior 1/3 of vocal cord	+2
Middle 1/3 of vocal cord	+3
Anterior 1/3 of vocal cord	+4
Anterior commissure	+5

This evaluated at the end of 3rd month of the treatment. Patients with scores above 8 were considered not to benefit from treatment and these patients were directed to surgery

Results

The mean age of the patients was 58.75 (range 35–79) years. The five (20.8%) women and 19 (79.2%) men were divided into four subgroups based on smoking habits: non-smokers ($n=9$, 37.5%), smokers 0–10 packs/year ($n=6$, 25%), 11–20 packs/year ($n=5$, 20.8%), and 21 + packs/year ($n=4$, 16.7%). Four patients consumed alcohol (16.7%).

Compared with before treatment (30.58), the RSI was significantly ($p<0.05$) lower at the 3- (24.17 mean) and 6- (20.04 mean) month follow-ups. The reflux finding score (RFS) also decreased significantly ($p<0.05$) from the first examination (8125) to those at 3 (6208) and 6 (4667) months.

In group 1, the difference between the RED values for all laryngeal regions between the initial examination and at 6 months was significant ($p<0.05$), while there were no significant differences between the GREEN and BLUE values, except for the right piriform sinus.

In group 2, the RED values were significantly ($p<0.05$) different only for the right pyriform sinus and the right and left vocal cords between the first examination and at 6 months. No significant results were obtained for any of the other RGB values.

Overall, seven (29.2%) patients showed a complete response, 12 (50%) showed a partial response, and five (20.8%) showed no response. The unresponsive patients were directed to surgery after 3 months (group 2). No recurrence was observed in any of group 2 patients after the 3-month follow-up.

Discussion

There are several reports on the clinical classification of vocal cord leukoplakia. Lee et al. classified the lesions of vocal cord leukoplakia into superficial, exophytic, and

ulcerative lesions [3]. Fang et al. classified the lesions based on their morphology, including colour, texture, size, hyperaemia, thickness, and symmetry [4]. Chen et al. divided the lesions into three groups: flat and smooth; elevated and smooth; and rough [5]. In these studies, lesions were classified as low and high grade and treatment decision was made according to this classification. In our study, we used two examination scales to make the treatment decisions. These scales included the patient demographics and morphological features of the lesions.

In the literature, 46–61% of lesions with leukoplakia have been reported as non-dysplastic [6, 7]. In the follow-up (mean 30 months) 3.8% of non-dysplastic lesions showed malignant transformation [8]. However, the rate of severe dysplasia and squamous cell carcinoma was reported as 15% at initial biopsies [8]. Therefore, we believe that lesion-specific treatment approaches need to be developed.

The laryngeal mucosa is thin and susceptible to damage. Laryngeal damage due to LFR occurs as a result of the drop in pH and gastric acid, pepsin, bile salts, and pancreatic enzyme in the reflux [9]. Pepsin, which is active at acidic pH, digests the proteins that form intercellular bonds, causing an increase in intercellular distance. In an experimental animal model, LFR significantly reduced the number of desmosomes in the laryngeal mucosa [10]. Increasing distance increases the permeability of water and ion channels, increasing the penetration into the cell and reducing the osmotic force of the cell. This triggers an inflammatory response [11]. The effect of the reflux contents on the laryngeal mucosa is similar to the effects of other inflammatory factors (poor voice use, chronic cough, vomiting, and recurrent infections). As a result, environmental carcinogens, such as cigarette by-products and alcohol, may have greater effects. In addition, oxidative stress resulting from chronic inflammation causes an increase in free oxygen radicals and hyperexpression of tumour markers, such as EGFR 16–18 and Cox-2 [12]. Taurocholic and glycocholic acids in alkaline reflux conjugate with nitrites in food to become *N*-glycocholic and *N*-taurocholic acids, which are also carcinogenic and mutagenic [13].

The laryngeal biopsy specimens from vocal cord leukoplakia and laryngeal carcinoma patients have significantly increased pepsin levels [11, 12]. Another study found that the number of LFR episodes and acid reflux exposure time in patients with laryngeal leukoplakia and glottic carcinoma were significantly higher than in a control group [16]. Other studies have reported an increased incidence of laryngeal carcinoma in LFR patients (68–72%) [17]–[19].

The PPI activity in LFR treatment is approximately 70% [20]. It is important to take a PPI twice a day, because no PPI suppresses the gastric acid for more than 16 h [21]. Rabeprazole was superior to placebo at improving LFR symptoms after 12 weeks of use [22]. PPI treatment is necessary for at least 2 months to eliminate LFR symptoms and for 6 months to improve laryngeal mucosal damage [23]. In our study, the patients also took the PPI for 6 months.

Non-surgical treatment may be effective for eliminating or reducing the size of vocal cord leukoplakia lesions. Almadori et al. reported 28 and 43% partial and complete response rates in 43 patients with vocal cord leukoplakia taking folic acid 5 mg three times daily for 6 months [24]. Papadimitrakopoulou et al. administered oral isotretinoin, oral alpha tocopherol, and subcutaneous interferon alfa to 36 patients with laryngeal precancerous lesions. After 12 months, they reported that the histopathological response rate was 48% and the clinical response rate was 57% [25]. Andrographolide is obtained from the herb *Andrographis paniculata* and has anti-inflammatory and anticancer properties. Xu et al. treated 41 patients with vocal cord leukoplakia with andrographolide and observed an 85 and 15% complete and partial response rates after 12 months [26].

In a study using conservative options [voice rest, smoking and alcohol abstinence, inhaler glucocorticoid therapy (budesonide 2 mg), and empirical PPI therapy (omeprazole 20 mg)] to treat benign vocal cord lesions, the mucosal elasticity and normal cord vibration improved [27]. In another study, 178 patients with vocal cord leukoplakia underwent non-surgical treatment, including smoking and drinking cessation, strict voice rest, 20 mg omeprazole twice daily and Chinese medication (Xuanbo Shuangsheng granules 8 g twice daily) for 6 weeks. At the end of the study, 127 of 178 patients (71.3%) had complete or partial responses [5]. In a patient with vocal cord leukoplakia, the lesion disappeared and the mucosal fluctuations and cord vibration function normalised with PPI treatment for 2 years; the treatment was continued and no recurrence was observed at 2.5 years [28].

In our study, 24 patients with vocal cord leukoplakia took 20 mg rabeprazole twice daily and 79.2% had complete or partial responses after 6 months. In addition, the unresponsive patients directed to surgery and no recurrence was observed with this treatment 3 months postoperatively in this group. But it is unclear if this outcome was related to surgery or to medical treatment.

The limitations of our study are the short follow-up period and small number of patients enrolled.

Conclusion

There is no standardised treatment algorithm for vocal cord leukoplakia. Consequently, the treatment options may vary and surgical treatment is often preferred. However, most vocal cord leukoplakia lesions have a low risk of malignancy. There is yet no objective measurement to replace the biopsy to predict malignant potential. However, we think that this risk can be predicted by evaluating the

lesion characteristics and taking into account the risk factors of the patient. Nevertheless, we believe that the lesion should be biopsied in suspected cases of malignancy potential. Since the possibility of malignancy progresses after the first biopsy, patient follow-up should be continued. Frequent follow-up is required in the lesions followed without biopsy. In this study, we developed a standardised treatment algorithm for vocal cord leukoplakia, to help in making treatment decisions. We treated the patients who were evaluated as appropriate for non-surgical treatment with a proton pump inhibitor and observed good treatment results. This method may benefit for selected patients. However, the treatment needs to be evaluated in randomised controlled clinical trials before it can be adopted widely.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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