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Original Article

Comparing suspension laryngoscopic mucosal dissection and plasma resection for laryngeal leukoplakia: prognostic outcomes

Ye Liu, Guihua Xia, Shaosheng Liu, Ke Ji

Department of Otolaryngology, Ningbo Beilun People's Hospital, Ningbo 315000, Zhejiang, China

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Abstract: Objective: The current research was designed to compare the clinical efficacy of suspension laryngoscopic mucosal dissection and plasma resection in the management of laryngeal leukoplakia and their effects on patient prognosis. Methods: Retrospective analysis was conducted on 184 laryngeal leukoplakia patients treated in Ningbo Beilun People's Hospital from January 2018 to October 2021. Based on the inclusion and exclusion criteria, 128 eligible patients were included, including 64 patients who underwent suspension laryngoscopic mucosal dissection (control group) and 64 patients who underwent cryolyrectomy (study group). The operative time, intraoperative bleeding volume, and time of pseudomembrane detachment in the two groups were recorded. Enzyme-linked immunosorbent assay (ELISA) was used to determine the serum concentrations of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, interferon-γ (IFN-γ), and IL-17A at 24 hours after surgery. Postoperative follow-up was conducted for one year. Results of the noise acoustic testing and stroboscopic laryngoscopy, including noise/harmonic ratio, amplitude perturbation, fundamental frequency perturbation, vocal fold vibration symmetry, and vocal fold mucosal wave, were documented before treatment and three months after treatment. The cumulative recurrence rate of patients within one year after surgery was recorded, and the cumulative recurrence rate of patients within 1 year after surgery was compared between the two groups. Results: Cryo-plasma resection significantly contributed to shorter operative time and less intraoperative bleeding volume as compared with suspension laryngoscopic mucosal dissection (both $P<0.05$), while time-lapse before postoperative pseudomembrane detachment was similar between the two groups ($P>0.05$). Patients with cryo-plasma resection exhibited significantly milder postoperative inflammatory response than those with suspension laryngoscopic mucosal dissection, as evinced by the lower serum concentrations of IL-2, IL-6, TNF-α, IFN-γ and IL-17A at 24-h in patients with cryo-plasma resection after operation ($P<0.05$), while the levels of IL-4 and IL-10 were similar between the two groups ($P>0.05$). At 3 months after operation, cryo-plasma resection contributed to more significant reductions of noise/harmonic ratio, amplitude perturbation, fundamental frequency perturbation, vocal fold vibration symmetry, and vocal fold mucosal as compared with suspension laryngoscopic mucosal dissection ($P<0.05$). Cryo-plasma resection contributed to a significantly lower incidence of cumulative recurrence than suspension laryngoscopic mucosal dissection ($P<0.05$). Multivariate analysis revealed no statistical difference in the impact of gender, age, smoking, and alcohol consumption on the recurrence and malignant transformation of laryngeal leukoplakia ($P>0.05$). Conclusion: Both suspension laryngoscopic mucosal dissection and plasma resection can provide significant efficacy in the treatment of laryngeal leukoplakia, and cryo-plasma resection can contribute to a lower incidence of relapse, enhanced postoperative recovery, and superior short- and long-term outcomes than plasma resection.

Keywords: Suspension laryngoscopic mucosal dissection, plasma resection, laryngeal leukoplakia

Introduction

Laryngeal leukoplakia is a condition characterized by the hyperplasia and hyperkeratosis of the laryngeal mucosa epithelium, leading to the formation of white patches or patchy bulges on the surface of the laryngeal mucosa, with occasional reddish lesions [1]. The disease is associated with various risk factors, including laryngeal reflux disease, chronic tobacco and alcohol use, improper voice usage, exposure to carcinogens, and compromised immunity [2, 3]. Patients often present with hoarseness as the initial symptom, along with a foreign body sen-

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sation in the pharynx, chronic cough, and sometimes itching and burning sensations in the larynx, as well as coughing up white keratinized material [4]. Conservative treatments are commonly adopted for mild to moderate cases, but when these fail, surgical intervention becomes necessary to manage the disease.

Both suspension laryngoscopic mucosal dissection and plasma resection are established surgical approaches to enhance or restore voice function while removing the leukoplakic lesions [7, 8]. However, the clinical progress in treating laryngeal leukoplakia still poses some challenges, particularly concerning postoperative voice function recovery and the risk of disease recurrence [9].

The current clinical management of laryngeal leukoplakia has shown promising outcomes, especially with the use of conservative treatments such as voice rest, avoidance of adverse stimuli, and medication to reduce inflammation [5, 6]. Additionally, surgical approaches have proven effective in cases where conservative treatments are insufficient. Suspension laryngoscopic mucosal dissection and plasma resection are both extensively adopted, but each method has its advantages and limitations.

The current treatment options are disadvantageous for the complexity of surgery, potential damage to healthy tissue during the removal of lesions, and possible adverse effects on postoperative voice function. Moreover, postoperative recurrence remains a significant concern, as the disease can relapse even after successful removal of the leukoplakic lesions.

The innovation of this study lies in its direct comparison of two common surgical approaches, suspension laryngoscopic mucosal dissection and plasma resection, to evaluate their clinical efficacy and impact on patient prognosis. By assessing factors such as operation time, intraoperative bleeding volume, postoperative recovery, inflammatory response, and recurrence rates, this study aims to provide valuable insights into the advantages and limitations of each surgical technique. Understanding these differences can help clinicians make informed decisions about the most appropriate treatment for individual patients, contributing to improved outcomes and better voice function recovery, as well as a lowered risk of disease recurrence.

Materials and methods

Sample source

The data of 184 patients with laryngeal leukoplakia treated in Ningbo Beilun People's Hospital from January 2018 to October 2021 were analyzed retrospectively. The present study was approved by the Ningbo Beilun People's Hospital Medical Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who were diagnosed with laryngeal leukoplakia by biopsy and had failure in ineffective conservative treatment [10]; (2) Patients who were highly suspected of severe heterogeneous hyperplasia or cancer and could have pathological examination after resection of lesions; (3) Patients with detailed clinical research data; (4) Patients with good cooperation.

Exclusion criteria: (1) Patients with a history of laryngeal surgery; (2) Patients with other organic lesions of vocal cords; (3) Patients with severe cardiac, liver or renal insufficiency; (4) Patients who were unable to complete follow-up.

Sample screening

According to the inclusion and exclusion criteria, a total of 128 patients who met the requirements were included. Among them, 64 patients who received suspension laryngoscopic mucosal dissection were assigned to the control group, and 64 patients who received cryolyrectomy were assigned to the study group.

Treatment methods

All patients were educated about protection against pharyngeal diseases, and they abstained from smoking and alcohol, and maintained a healthy diet and good emotion after admission. Each patient received preoperative blood tests, clotting time test, prothrombin time test, and electrocardiogram. Intraoperatively, the patient was placed in the supine position and was given general anesthesia with tracheal intubation, and the teeth were protected by dental pads.

Patients in the control group underwent suspension laryngoscopic mucosal dissection. (1) After the supporting laryngoscope with an

endoscope was sent to the larynx to fully reveal the vocal folds, the supporting frame was fixed, and the operative area was magnified under the surgical microscope; (2) The needle electric knife was adopted to mark the electrocoagulation at 5 mm outside the edge of the lesion, and submucosal saline was injected outside the mark until the lesion was obviously elevated to allow electrocuting; (3) The high-frequency electric coil sleeve was opened with the opening completely placed on the elevated part of the lesion for compression and aspiration, so that the root of the lesion and the surrounding part of the normal mucosa were covered; (4) With the high-frequency electric generator turned on and the electric cutting index adjusted to 3, peeling and excision were performed with electric cutting current. After the lesion was resected, the procedure was concluded after hemostatic treatment.

Patients in the study group underwent cryoplasma resection. (1) The laryngoscope was delivered to the larynx through the mouth, pharynx, and epiglottis to fully expose the laryngeal cavity operation area, and the laryngoscope was fixed after determining the location and extent of the lesion; (2) The low-temperature plasma knife head was bent into an arc, with the cutting parameters adjusted to 7 gears and the coagulation parameters adjusted to 4 gears for resection of the diseased mucosa; (3) For potentially fixed bleeding-prone areas, the plasma knife was maintained in the same position after resection and ablation, and replaced with a hemostasis gear for hemostasis, i.e., resection and hemostasis were performed in the same surgical site. All patients were given intravenous fluids promptly after surgery. Anti-edema and anti-inflammatory treatment were administered, and antibiotics and nebulized inhalation therapy were given for 1-3 d if necessary. Patients and their families were informed of postoperative precautions, and patients were kept in vocal abstinence for one week after surgery.

Outcome measures

The operative time, intraoperative bleeding volume, and time of pseudomembrane detachment of each patient were recorded. At 24 h after operation, 2 mL venous blood was extracted from each patient, and anticoagulated with ethylenediaminetetraacetic acid (EDTA). On the day of sample collection, the enzyme linked immunosorbent assay (ELISA) was used to detect interleukin (IL)-2 (Mlbio, Shanghai, China; ml058063), IL-4 (Mlbio, Shanghai, China; ml058093), IL-6 (Mlbio, Shanghai, China; ml058097), IL-10 (Mlbio, Shanghai, China; ml064299), tumor necrosis factor (TNF)-α (Mlbio, Shanghai, China; ml077385), interferon-γ (IFN-γ, Mlbio, Shanghai, China; ml077386) and IL-17A (Mlbio, Shanghai, China; ml058052) strictly according to the instructions of the corresponding kits. The decrease in the expression of these indicators represented a better reduction in inflammatory response. Voice analysis was carried out by the Dr. Speech Science for Windows instrument from Tiger DRS Inc. (Shanghai) under the condition of sound insulation and the ambient noise controlled below 45 dB (A). The subject was required to sit with an upright position and then the two electrodes of EGG were placed on the skin of the midpoint of the thyroid cartilage plates on both sides of the subject. The electrodes were fixed, and the head of subject was relatively fixed. With a distance of 5-10 cm from mouth to the microphone, the subject was required to send the vowel /a/ for 3 seconds each time. The voice signal was input, amplified and converted through A/D by microphone to display sound waves. The middle stationary segment was selected to analyze the voice and EGG signal. The segment was then magnified and inputted into the computer and analyzed three times. The acquired parameters were averaged. A stable EGG waveform was selected from the obtained EGG signal. The results of noise acoustics and stroboscopic laryngoscope before and 3 months after treatment were recorded, including noise/harmonic ratio, amplitude perturbation, fundamental frequency perturbation, vocal fold vibration symmetry and vocal fold mucosal wave. The score of vocal fold vibration symmetry is 0-3. A higher score indicates more serious vocal fold vibration asymmetry. The vocal fold mucosal wave was divided into 0-5 points, and a higher score indicates more serious disappearance of vocal fold mucosal wave [11]. Based on electronic pathology and outpatient reexamination records, the cumulative recurrence rate of patients within one year was calculated.

Statistical analysis

The data of both groups were analyzed by SPSS 19.0. The measurement data were expressed as (mean ± SD); the t-test was used for inter-

Table 1. Patient characteristics

Groups	Gender		Age (year)	Disease duration (month)	History of smoking and drinking			Lesion location		
	Male	Female			Smoking	Drinking	Smoking and drinking	Right vocal cord	Left vocal cord	Double vocal cord
Control group (n=64)	42	22	45.82±8.30	8.92±4.16	38	21	5	24	27	13
Study group (n=64)	40	24	46.22±8.15	8.75±4.36	39	19	6	26	28	10
t/x^2	0.136		0.275	0.226	0.099			0.477		
p	0.713		0.784	0.822	0.752			0.490		

Table 2. Surgical indices (mean ± SD)

Groups	Intraoperative bleeding volume (ml)	Operation time (min)	Time-lapse before pseudomembrane detachment (d)
Control group (n=64)	15.10±2.18	65.53±10.06	6.88±1.64
Study group (n=64)	5.27±2.62	50.20±8.28	7.05±1.56
T	23.073	9.413	0.601
P	<0.001	<0.001	0.549

group comparison, and paired t-test was used for intra-group comparison. Count data were expressed as cases (%) and analyzed using the χ^2 test. Statistical significance was indicated by P<0.05.

Results

Patient characteristics

The control group consisted of 42 males and 22 females, with a mean age of (45.82±8.30) years, mean disease duration of (8.92±4.16) months, including 38 cases of smoking, 21 cases of drinking, 5 cases of smoking + drinking; among them, 24 cases of lesions located in the right vocal cord, 27 cases in the left vocal cord, and 13 cases in both vocal cords. The study group consisted of 40 males and 24 females, with a mean age of (46.22±8.15) years, mean disease duration of (8.75±4.36) months, including 39 cases of smoking, 19 cases of drinking, 6 cases of smoking + drinking; among them, 26 cases of lesions located in the right vocal cord, 28 cases in the left vocal cord, and 10 cases in both vocal cords. The two groups were not significantly different in terms of patient characteristics (all P>0.05) (**Table 1**).

Surgical indices

Cryo-plasma resection contributed to markedly shorter operation time and less intraoperative bleeding volume as compared with suspension laryngoscopic mucosal dissection (P<0.05), while time-lapse before postoperative pseudomembrane detachment was similar between the two groups (P>0.05) (**Table 2**).

Inflammatory factor levels

There was no statistical difference in the preoperative levels of IL-2, IL-4, IL-6, IL-10, TNF-α, INF-γ, and IL-17A between the two groups of patients (all P>0.05). All indicators were significantly reduced in both groups after treatment (all P<0.001). The postoperative inflammatory reaction in the study group was significantly milder than that in the control group, and the serum levels of IL-2, IL-6, TNF-α, interferon-γ, and IL-17A were lower than those in the control group at 24 h postoperatively (all P<0.05), whereas there was no significant difference in the levels of IL-4 and IL-10 between the two groups (both P>0.05) (**Figure 1**).

Acoustic noise test results and stroboscopic laryngoscopy results

At 3 months after treatment, cryo-plasma resection contributed to a more significant reduction of noise/harmonic ratio, amplitude perturbation, fundamental frequency perturbation, vocal fold vibration symmetry and vocal fold mucosa than suspension laryngoscopic mucosal dissection (all P<0.05) (**Table 3**).

Cumulative recurrence

In the control group, there were 2 patients who underwent vertical partial laryngectomy for cancer and 5 patients who underwent laryngoscopic mucosal resection for recurrence, and the remaining 57 patients were followed up and showed on recurrence. In the study group, there was no carcinoma and one patient who recurred and underwent cryoplasma resection again,

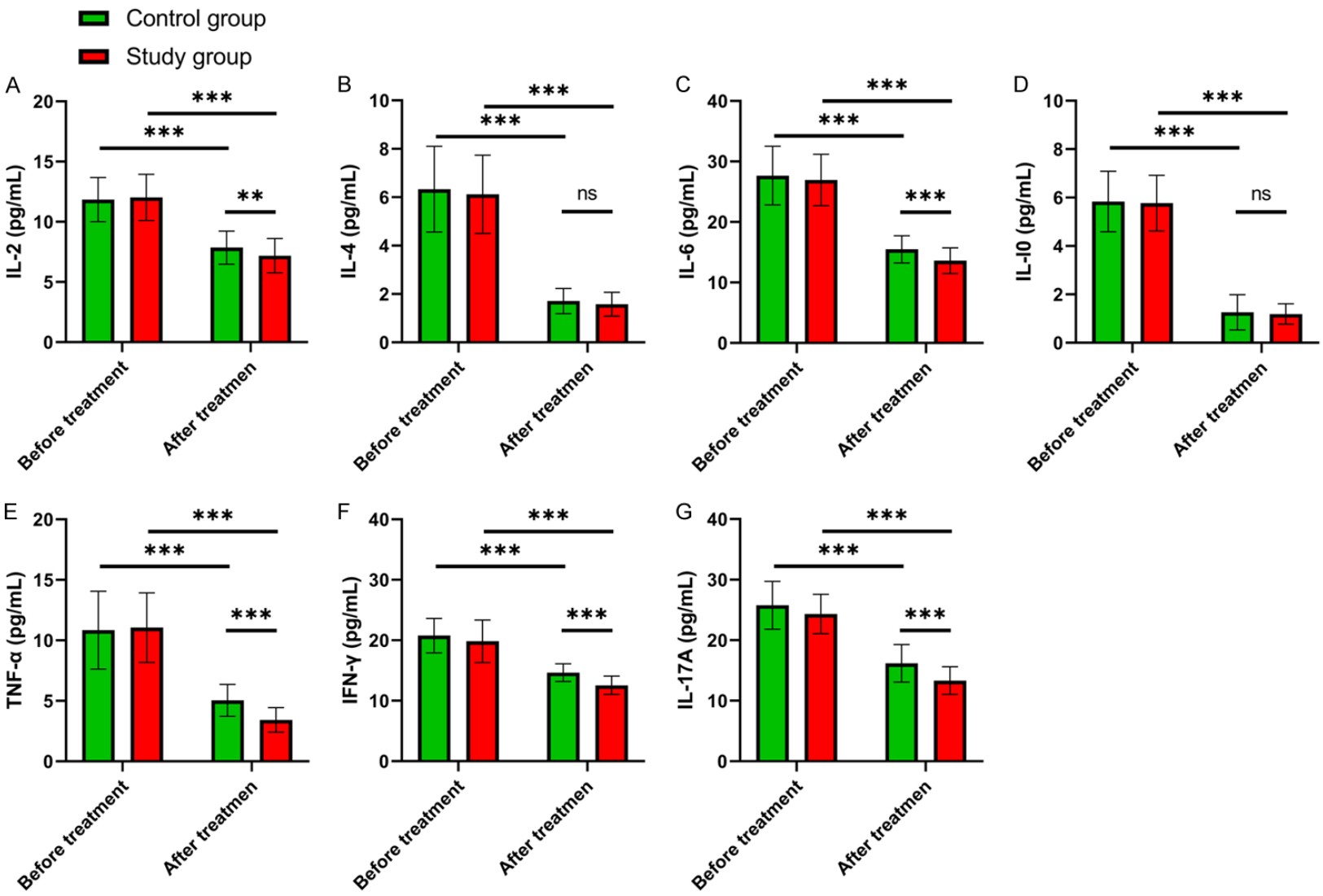

Figure 1. Changes in inflammatory indexes before and after treatment of patients. A. Changes in IL-2 levels before and after treatment in the two groups. B. Changes in IL-4 levels before and after treatment in both groups. C. Changes in IL-6 levels before and after treatment in both groups. D. Changes in IL-10 levels before and after treatment in the two groups. E. Changes in TNF-α levels before and after treatment in the two groups. F. Changes in INF-γ levels before and after treatment in both groups. G. Changes in IL-17A levels before and after treatment in both groups. Note: ns P>0.05, **P<0.01, ***P<0.001; IL-2 (Interleukin-2), IL-4 (Interleukin-4), IL-6 (Interleukin-6), IL-10 (Interleukin-10), TNF-α (Tumor necrosis factor alpha), INF-γ (Interferon gamma) and IL-17A (Interleukin-17A).

Table 3. Acoustic noise test results and stroboscopic laryngoscopy results (mean ± SD)

Groups		Control group (n=64)	Study group (n=64)	*t*	*P*
Noise/Harmonic Ratio (dB)	Preoperatively	0.24±0.10	0.23±0.11	0.538	0.592
	3 months postoperatively	0.15±0.05	0.07±0.03	10.976	<0.001
Amplitude perturbation (%)	Preoperatively	10.49±3.04	10.65±3.01	0.299	0.765
	3 months postoperatively	5.87±1.56	5.02±1.00	3.670	<0.001
Fundamental frequency perturbation (%)	Preoperatively	2.06±0.85	2.03±0.87	0.197	0.844
	3 months postoperatively	0.80±0.25	0.52±0.20	6.997	<0.001
Vocal fold vibration symmetry (min)	Preoperatively	2.24±0.66	2.22±0.70	0.166	0.868
	3 months postoperatively	0.58±0.10	0.32±0.08	16.242	<0.001
Vocal fold mucosal wave (min)	Preoperatively	3.45±0.81	3.39±0.78	0.427	0.670
	3 months postoperatively	0.88±0.12	0.56±0.07	18.427	<0.001

Table 4. Relationship between recurrence, malignant transformation, and clinical factors [n (%)]

Factor	Relapse + Malignancy (n=8)	No Relapse + Malignancy (n=120)	t/x^2	*p*
Gender				
Male	4	78	0.733	0.391
Female	4	42		
Age (year)	48.44±3.81	45.52±8.92	0.919	0.359
Disease duration (month)	8.41±1.82	8.79±4.93	0.217	0.828
Smoking				
Yes	3	74	1.827	0.176
No	5	46		
Drinking				
Yes	2	38	0.155	0.693
No	6	82		
Smoking and drinking				
Yes	2	38	0.155	0.693
No	6	82		
Lesion location				
Right vocal cord	1	10	0.165	0.920
Left vocal cord	3	47		
Double vocal cord	4	63		

and the remaining 63 patients were followed up and showed no recurrence. Cryo-plasma resection resulted in a significantly lower incidence of cumulative recurrence as compared with suspension laryngoscopic mucosal dissection (P<0.05).

The relationship between recurrence, malignant transformation, and clinical factors

According to univariate analysis, the impact of gender, age, smoking, and alcohol consumption on the recurrence and malignant transformation of leukoplakia surgery patients was not statistically significant (all P>0.05), as shown in **Table 4**.

Discussion

The rise in otorhinolaryngological conditions, such as chronic tonsillitis, allergic rhinitis, epiglottis cysts, and adenoid hypertrophy, are attributed to factors including poor eating habits, inconsistent work routines, work-related stress, and environmental contamination [12, 13]. Existing studies suggest that laryngeal leukoplakia commonly afflicts the middle-aged and elderly demographics, with an estimated prevalence rate of 0.07%-0.21% and an overall prevalence of 1%-6%. The disease is notably more prevalent among men than women [14]. Clinically, it has been observed that older patients with laryngeal leukoplakia typically

exhibit more pronounced manifestations and a high degree of pathological diversity. Consequently, age is deemed by many researchers as one of the most significant risk factors for this disease [15]. Epidemiological investigations indicate that vocal cord leukoplakia is most frequently seen in men over 40 years old, with a male-to-female ratio of approximately 4.6:1.0. The incidence of vocal cord leukoplakia correlates with habits of smoking and alcohol consumption.

However, the statistical analysis in this study revealed that gender, age, smoking, and alcohol consumption were not independent risk factors for the recurrence or malignant transformation of vocal cord leukoplakia. This condition has the potential to progress into a precancerous stage of laryngeal squamous cell carcinoma. Thus, prompt surgical intervention becomes necessary after the failure of conservative treatment to induce disease regression, thereby mitigating its malignancy rate [16]. With the evolving understanding of trauma surgery, low-temperature plasma technology is increasingly being implemented in the field of otolaryngology. Plasma refers to the liberation of electrons from atoms into a highly ionized state that possesses sufficient energy to disrupt the molecular bonds of organic molecules in tissue. This process results in the separation of molecules, which facilitates tissue coagulation, necrosis, detachment, and precise, direct excision [17, 20]. In the present study, compared with suspension laryngoscopic mucosal dissection, plasma resection significantly reduced the operation time and intraoperative blood loss. However, there was no significant difference in the time of postoperative pseudomembrane detachment between the two groups. Notably, patients undergoing plasma resection showed obviously milder postoperative inflammatory reaction, namely, lower serum concentrations of IL-2, IL-6, TNF-α, IFN-γ and IL-17A at 24 hours after operation. However, the concentrations of IL-4 and IL-10 were similar between the two groups. IL-2 is a cytokine, which is mainly produced by activated T cells. It plays a role in the proliferation and differentiation of T cells, the core of immune response. The decrease of postoperative IL-2 concentration indicates that the degree of immune system activation in patients undergoing plasma resection is not so obvious [21]. The increase of IL-6 level is common in cases with surgical trauma or tissue injury. Its low level after plasma resection indicates that the tissue damage or trauma caused in this procedure may be lighter than that caused by alternative surgical techniques [22]. TNF-α is an important inflammatory mediator, which can trigger fever, inflammation and apoptosis (programmed cell death). The decrease of TNF-α level after operation suggests weakened inflammatory response is [23]. IFN-γ, mainly produced by natural killer (NK) cells and T cells, has immunomodulatory and antiviral functions. The decrease of postoperative IFN-γ level suggests that plasma resection can better control immune activation [24]. IL-17A is related to autoimmune diseases, which has been verified to play a role in inducing and regulating pro-inflammatory response [25]. The decrease of IL-17A level indicates relatively small immune-mediated tissue damage.

In a retrospective analysis conducted by Yang SW et al [16], cryo-plasma resection also contributed to favorable outcomes, with shorter operation time, reduced intraoperative bleeding, and lower levels of inflammatory factors compared to suspension laryngoscopic mucosal dissection. This advantage is attributed to plasma resection's ability to achieve hemostasis concurrently with lesion removal, resulting in minimal intraoperative bleeding, reduced invasive pain, and mild postoperative side effects. These benefits collectively contribute to expedited wound healing [19]. Moreover, three months postoperatively, cryo-plasma resection led to a more significant improvement in noise/harmonic ratio, amplitude perturbation, fundamental frequency perturbation, vocal fold vibration symmetry, and vocal fold mucosal wave when compared with suspension laryngoscopic mucosal dissection. The cumulative recurrence rate was also significantly lower following cryo-plasma resection. This finding aligns with the results of a similar study carried out by Hao F et al [26]. The low-temperature (40-70 degrees) application of plasma technology to remove diseased tissue is noteworthy. Because the current does not flow directly through the tissue and produces a thermal effect on the skin without vaporizing the tissue, contributing to effective reduction of damage to the tissue [27]. The decrease of this tissue damage may be one of the reasons for the decrease of the concentration of proinflam-

matory factors after operation. Less tissue damage means less inflammatory signals, resulting in less inflammatory cells being recruited to the site. In addition, the ability of plasma resection to stop bleeding while removing lesions minimizes intraoperative bleeding, which can further help reduce inflammation. Blood and its components outside blood vessels will produce high inflammation. Although there was no significant difference between the two groups in anti-inflammatory cytokines IL-4 and IL-10, the decrease of proinflammatory cytokines in the group given plasma resection highlights the superiority of this technique in reducing inflammation and tissue trauma.

However, this study has some limitations. First, the limitation of this study is the short follow-up period. Future trials with longer follow-up are needed to validate these results and provide higher quality evidence for the treatment of laryngeal leukoplakia. Second, the small sample size of this study may impact the results of multivariate analysis. Larger sample size is needed in future studies to increase the reliability of the results. We hope that more experiments can be conducted in future research to address these limitations.

Conclusion

Both suspension laryngoscopic mucosal dissection and plasma resection provide significant efficacy in the treatment of laryngeal leukoplakia. Cryo-plasma resection contributes to a lower incidence of relapse, enhanced postoperative recovery, and superior short- and long-term outcomes.

Disclosure of conflict of interest

None.

Address correspondence to: Ye Liu, Department of Otolaryngology, Ningbo Beilun People's Hospital, 1288 Lushan East Road, Beilun District, Ningbo 315000, Zhejiang, China. Tel: +86-15057469685; E-mail: vickyly80@126.com

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