

Treatment Results of Vocal Process Granuloma: Intubation versus Contact Granuloma

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Abstract

Introduction Contact granulomas (CGs) and intubation granulomas (IGs) are known to have different clinical manifestations despite having the same pathological features.

Objective The purpose of the present study was to analyze the treatment results for CG and IG and to obtain clinical information.

Methods We retrospectively reviewed the medical records of patients diagnosed with vocal process granuloma (VPG) between January 2015 and December 2018. The patient's age, sex, medical history, lesion size, lesion type, reflux finding score (RFS), response to treatment, duration of treatment, and follow-up period were compared.

Results Eighteen patients with CG and 14 patients with IG were included in the study. The IG group had more female patients ($p = 0.0009$), showed better response to proton pump inhibitor (PPI) and steroid inhalation (SI) ($p = 0.036$), and had a shorter treatment period ($p = 0.0029$) than the CG group. Five patients who received botulinum toxin injections in their vocal cords had complete remission.

Conclusion Compared with CG, IG was more responsive to treatment with PPI and SI and required a shorter duration of treatment.

Keywords

- ▶ vocal cord
- ▶ contact
- ▶ intubation
- ▶ proton pump inhibitor
- ▶ botulinum

Introduction

Vocal process granulomas (VPGs) are benign lesions of the larynx, typically including intubation granulomas (IGs) and contact granulomas (CGs).^{1,2} There is no pathological difference between IG and CG; however, cases of IG clinically occur after intubation, while cases of excessive glottic contact are referred to as CGs. Major causes of VPG include voice abuse, endotracheal tube intubation, gastroesophageal reflux, and chronic cough. If no relevant factors are identified, the cause is considered unknown.^{3–6} Rather than each factor being an isolated cause, these factors can interact and compound their effects, resulting in vocal process granulomas.^{7,8} At this time,

if there is a history of endotracheal tube intubation, it is clinically diagnosed as IG; if not, it is diagnosed as CG. Intubation granuloma may have different clinical features from CG because IG includes physical and direct factors, such as scratching damage to the mucosa of the arytenoid cartilage that can occur during endotracheal intubation or from pressure necrosis during tube maintenance. However, because VPG is an uncommon disease and, in the absence of any standardized treatment, various treatments are performed according to the preference of the physician, few studies have compared the clinical features and treatments of CG and IG. The purpose of the present study is to analyze the treatment results for IG and CG and to obtain clinical information.

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Materials and Methods

Analysis of Patient Information

The current study was performed through a retrospective review and analysis of medical records of patients diagnosed with VPG from January 2015 to December 2018. The research protocol was approved by the Institutional Clinical Research Ethics Center (GDIRB2019–352). Each VPG case was diagnosed by laryngoscopy and categorized into CG and IG groups according to the history of airway intubation. Only patients whose progression was completed by one otolaryngologist following the same treatment protocol were included. The age, gender, medical history, granuloma size and type, treatment method, duration of treatment, treatment response, and follow-up period were analyzed through the medical records. Comparisons were made between the CG and IG groups. The granulomas were classified as small, medium, or large according to their size (►Fig. 1) and were further classified by type as granulomatous and ulcerative. The reflux finding score (RFS) was analyzed through laryngoscopic imaging by two otolaryngologists who were blinded to the study, and their scores were averaged.

Analysis of Treatment Results

Each patient's course of treatment was prospectively managed by one otolaryngologist with the same treatment protocol. All patients were treated with proton pump inhibitors (PPIs) and oral steroid inhalers (SIs) as primary medications. Intracordal botulinum toxin injections (BTXs) were administered to patients who did not respond to these medications. Intracordal BTXs were administered percutaneously through the cricothyroid membrane during vocal cord observation using botulinum toxin (Type A [abobotulinumtoxinA] from *Clostridium botulinum*; Botox, Allergan plc, Dublin, Ireland). The injections were administered to only one vocal cord. If the granuloma was on one side, BTX was administered to the ipsilateral vocal cord. If the granuloma was on both sides, BTX was administered to the side with the larger granuloma. The amount of each injection was 4 IU. Determination of the treatment effect was "complete remission" (CR), when granulomas completely disappeared; "marked improvement" (MI), when a marked reduction in size of more than 50% occurred; "stationary" (ST), when a decrease in size of less than 50% or no change occurred; and

"progression" (PG), when there was an increase in the size of the granulomas. Finally, CR and MI were recorded as "responsive" when it was determined that there was a response to the treatment, and ST and PG were recorded as "unresponsive" as they were judged to be unresponsive to the treatment.

Statistics

To identify factors that may affect treatment outcomes, we compared age, gender, size and type of granuloma, RFS, duration of medication treatment, medication result, and final result of treatment between the CG and the IG lesions. A chi-squared test and a Mann-Whitney *U*-test were used to verify the differences between the two groups. Significant differences between the two groups were defined as those having *p*-values < 0.05. The RFS used was the average of the results of two trials by two otolaryngologists, and the Spearman correlation coefficient was used to analyze the correlation and relevance of the RFS between the examiners.

Results

Results of Demographic Analysis of Patient Data

In total, 61 patients were diagnosed with VPG during the study period, with 37 patients having CG and 24 patients having IG. Owing to not completing their follow-up evaluations, 28 patients were excluded from the study, as was a single patient who was diagnosed with tuberculosis. Finally, 18 patients with CG and 14 patients with IG were included in the study. The mean age of the CG group was 53.9 (\pm 12.5) years, and the median was 54 years. The mean age of the IG group was 44.1 (\pm 16.4) years, and the median was 43 years. There was no significant difference in the age between the two groups (*p* = 0.2089) (►Table 1). Of the 18 patients with CG, 15 were male (83.3%) and 3 were female (16.7%). Of the 14 patients with IG, 3 were male (15.4%) and 11 were female (84.6%). There was a significant difference in the sex distribution between the two diseases (*p* = 0.0009). Of the CGs, 8 were small, 5 were medium, and 5 were large. Of the IGs, 5 were small, 2 were medium, and 7 were large. There was no significant difference in the size of the granulomas between the two groups (*p* = 0.5148). There were 15 granulomatous and 3 ulcerative CGs. All 14 of the IGs were granulomatous. There was no significant difference in the types of

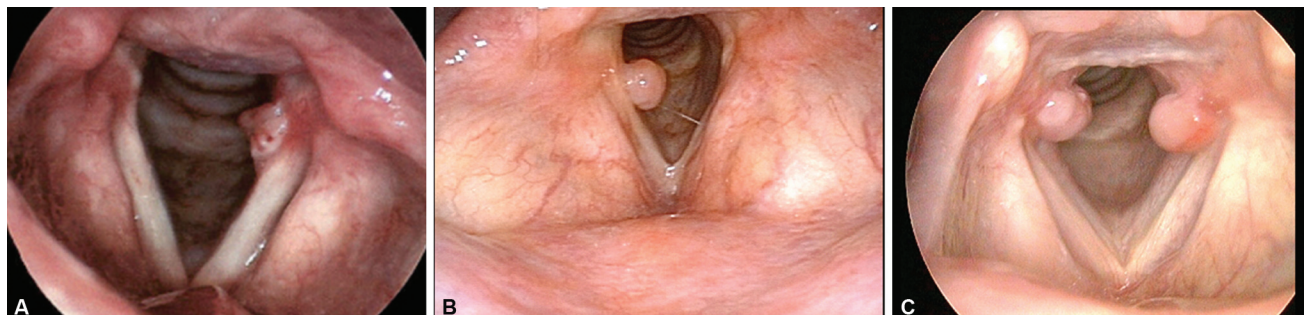


Fig. 1 Classification of granuloma. (A) Small, sessile, and granulomatous contact granuloma. (B) medium, pedunculated, and granulomatous contact granuloma. (C) Large, pedunculated, and granulomatous intubation granuloma.

Table 1 Demographic data of the patients with vocal process granulomas

Factors		Contact	Intubation	P-value
Number	(n)	18	14	
Age (years)	Mean (\pm SD)	53.9 (\pm 12.5)	44.1 (\pm 16.4)	0.2089
	Median (range)	54 (27–72)	43 (21–72)	
Gender	Male (n)	15	3	0.0009*
	Female (n)	3	11	
Granuloma size	Small (n)	8	5	
	Medium (n)	5	2	0.5148
	Large (n)	5	7	
Granuloma type	Granulomatous (n)	15	14	0.2379
	Ulcerative (n)	3	0	
Voice abuse	Yes (n)	6	0	1
	No (n)	12	0	
Reflux finding score	Mean (\pm SD)	9.4 (\pm 2.2)	8.1 (\pm 1.6)	0.1311
	Median (range)	8.5 (5.75–13.25)	7.75 (5–10.25)	

Abbreviation: SD, standard deviation.

* $P < 0.05$ in chi-squared test.

granulomas between the two groups ($p = 0.2379$). There were 6 patients with a history of vocal abuse, but this was only noted among the patients with CG. Of the 6 patients with a history of vocal abuse, 5 were male and a single patient was female. The patients in the IG group had no history of vocal abuse; therefore, statistical analysis was not meaningful. The mean value of RFS in the CG group was 9.4 (± 2.2), and the median was 8.5. The mean value of RFS in the IG group was 8.1 (± 1.6), and the median was 7.75. There was no significant difference in the RFS between the two groups ($p = 0.1311$). The intra-examiners' Spearman correlation coefficients (r) of the RFS were 0.7629 (95% confidence interval: 0.5570–0.8825; $P < 0.0001$) and 0.593 (95% confidence interval: 0.2982–0.7845; $p = 0.0003$), respectively, showing a positive correlation. The inter-examiner's Spearman correlation coefficient (r) was 0.6478 (95% confidence interval: 0.3722–0.8165; $P < 0.0001$) showing a positive correlation.

Results of Treatment

Seven of the 18 patients (38.9%) in the CG group showed a response to the combined medical treatment with a PPI and SI, with CR achieved in 4 patients and 3 patients demonstrating MI. The granulomas in 11 patients were considered unresponsive, with 10 of them determined to be stationary (ST) and one of them showing progression (PG). In the IG group, 11 out of 14 patients (78.6%) responded to the medical treatment and all 11 resulted in CR. Only 3 were considered unresponsive, and all 3 were determined to be ST. There was a statistically significant difference in the response to the combined medical therapy between the CG and IG groups ($p = 0.036$) (**Table 2**).

The mean duration of the combined medical treatment was 3.3 (± 1.7) months, and the median duration was 3 (2–9)

months in the CG group. In the IG group, the mean duration of the combined medical treatment was 2.0 (± 0.8) months, with a median duration of 2 (1–3) months. The duration of the combined medical treatment was significantly longer in the CG group than in the IG group ($p = 0.0029$).

Botulinum toxin injections were administered to five patients who did not respond to medication, including three patients in the CG group and two patients in the IG group. After BTX administration, CR was noted in all five patients (**Fig. 2**).

Finally, 10 patients (10/18, 55.6%) in the CG group and 13 patients (13/14, 92.9%) in the IG group responded to the treatment, and the final treatment response of the two groups showed a statistically significant difference ($p = 0.0443$) (**Fig. 3**).

The mean follow-up period in the CG group was 4.5 (± 2.5) months, and the median was 4 (2–12) months. The mean follow-up period in the IG group was 2.9 (± 1.8) months, and the median was 2.5 (1–6) months. The CG group had a significantly longer follow-up period than the IG group ($p = 0.0259$).

Discussion

The purpose of the present study was to evaluate the clinical features and treatment response of CGs and IGs. In terms of clinical features, IGs were more common in females than in males, as is known due to the vulnerability of females to IGs because of their relatively small larynx and thin mucosa.⁹

Previous studies have suggested that voice therapy and PPIs are recommended as the primary treatments for VPG. Surgery and BTX treatment are also used as adjuvant therapy.^{3,10,11} According to a recent meta-analysis on IGs, antireflux therapy, speech therapy, antiinflammatory drugs,

Table 2 Treatment results of the patients with vocal process granulomas

Results		Contact (n = 18)	Intubation (n = 14)	P-value
Medication result (n)	Responsive (CR/MI)	7 (4/3)	11 (11/0)	0.036*
	Unresponsive (ST/PG)	11 (10/1)	3 (3/0)	
	Odds ratio (95% CI)	0.1736 (0.03538–0.8518)		
Duration of medication (months)	Mean (\pm SD)	3.3 (\pm 1.7)	2.0 (\pm 0.8)	0.0029 [†]
	Median (range)	3 (2–9)	2 (1–3)	
Cases of Botox injection (n)		3	2	
Final result of treatment (n)	Responsive (CR/MI)	10 (7/3)	13 (13/0)	0.0443*
	Unresponsive (ST/PG)	8 (7/1)	1 (1/0)	
	Odds ratio (95% CI)	0.09615 (0.01027–0.9004)		
Follow-up period (months)	Mean (\pm SD)	4.5 (\pm 2.5)	2.9 (\pm 1.8)	0.0259*
	Median (range)	4 (2–12)	2.5 (1–6)	

Abbreviations: CI, confidence interval; CR, complete remission; MI, marked improvement; PG, progression; SD, standard deviation; ST, stationary.
* $P < 0.05$ in chi-squared test.

[†] $P < 0.05$ in Mann–Whitney U test.

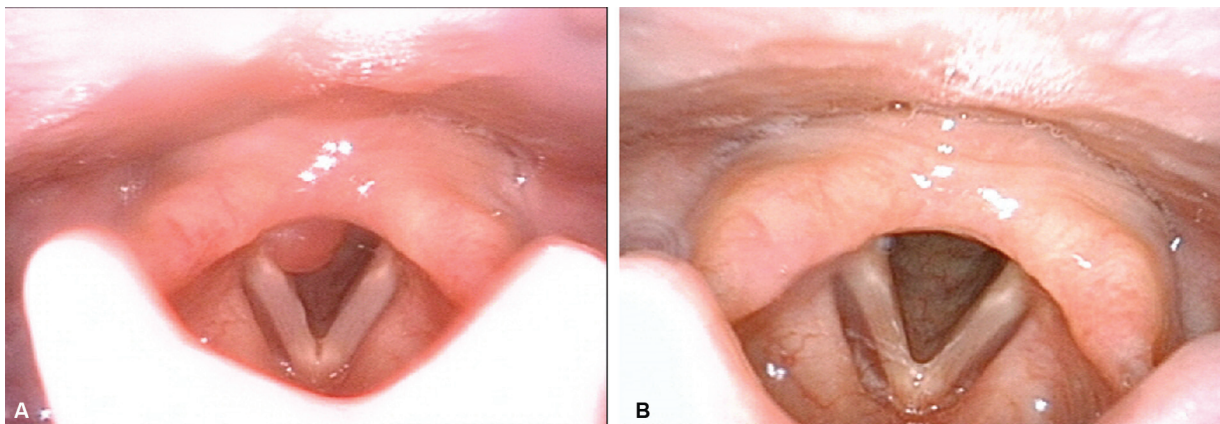


Fig. 2 A 21-year-old female patient who complained of voice changes after plastic surgery and underwent a botulinum toxin injection on a right vocal fold via the trans-cricothyroid membrane. (A) Before the botulinum toxin injection. (B) 3 months after botulinum toxin injection.

steroids, antibiotics, zinc sulfate, and surgery were all performed for IGs. It has been suggested that the treatment methods for CGs and IGs are similar.⁸ However, according to the results of the current study, the response to the combined medical treatment was different between the CG and IG groups, and the IG group showed better responsiveness to PPI and SI combination therapy than the CG group.

Since gastroesophageal reflux is known to be an important factor in VPG, PPIs are widely used to treat VPG to suppress the mucosal damage to the vocal cords caused by gastric acid reflux.^{7,8,12,13} Steroid sprays were able to reduce the local inflammation of the vocal cords, and one study reported that most IGs were treated with budesonide inhalation alone.¹⁴ Therefore, PPI and SI combination therapy were expected to be able to treat VPG through two different mechanisms. Based on this logic, Hillel et al.⁸ treated VPG with a combination of PPI and SI (triamcinolone acetonide 300 mcg 3 times per day) and reported that 57 of the 62 granulomas in 54 patients (69%) were cured. Of the 54

patients, 19 (24%) had a history of intubation, but there was no separate analysis of CG versus IG.

In the present study, PPI and SI were used primarily as the initial treatment for all cases of VPG. The effects of the combined medical treatment with PPI and SI were significantly different between the IG (11/14, 78.6%) and the CG groups (7/18, 37.5%). Compared with the CG, the IG group showed a better response because the endotracheal intubation that directly induced the physical stimulation in IG was temporary, and this causal factor was removed during treatment. However, CG occurred despite the absence of direct factors such as intubation. Therefore, it is likely that the main factors, such as vocal abuse, persisted uncontrolled.

The disadvantage of the present study was that the duration of medication treatment and/or the follow-up period was too short. However, a long treatment period does not mean that the results of the treatment were reliable. The study by Hillel et al.,⁷ mentioned earlier, involved a range of long-term medications with an average of 11 months of

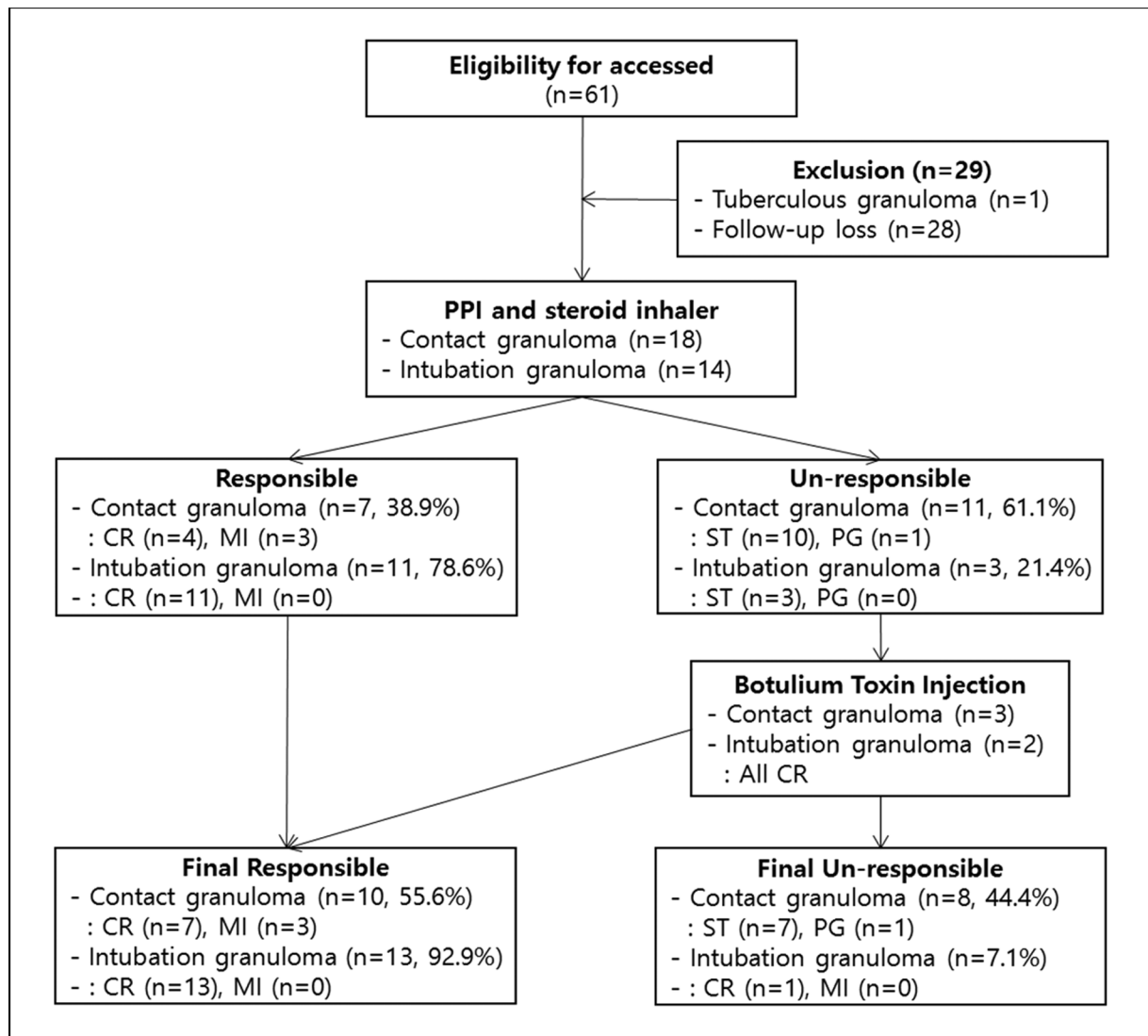


Fig. 3 Flow diagram of treatment for vocal cord granuloma.

treatment (ranging from less than 1 month to more than 48 months). The fact that the VPG, which initially did not respond to drug treatment, decreased after more than one year of treatment might have been due to factors other than the drug treatment, and it was difficult to know the degree of response to the drug treatment. According to Wang et al.,¹⁵ when 53 patients with VPG received follow-up evaluations without treatment, 44 patients (81%) were cured in an average of 7.5 months. There were 15 patients with IG among the 53 patients; the time to cure in patients with IG was 6 months on average and significantly shorter than that of patients with CG (average of 8.5 months). In other words, the long treatment period made it difficult to distinguish whether the treatment or natural healing was responsible for the cure.

In the current study, the patients with IG showed better response and needed a shorter duration of treatment than the patients with CG. Integrating this data with that from previous studies showed that IG had a better response to medication than CG, resulting in a higher cure rate and a shorter duration of treatment. Intubation granulomas could

also be spontaneously cured earlier than CG, even if left untreated.

In 1995, BTX was introduced by Nasri et al.¹⁶ to treat CG. Damrose et al.¹⁷ reported that percutaneous BTX was safe and effective in the treatment of refractory VPG. The therapeutic principle of BTX is that the patient recovers from the granuloma during the botulinum toxin-induced transient vocal cord paralysis, which reduces the tightening of the glottal gate and avoids contact with the contralateral arytenoid cartilage. Of the 14 patients who did not respond to the medication, 5 patients (3 patients with CG and 2 patients with IG) were completely cured after BTX treatment. Previous studies reported that BTX showed the best effect compared with other treatment options such as voice therapy, surgical removal, PPI, and SI for VPG.^{10,18,19} However, there is a risk of hoarseness or dysphagia after BTX treatment. Moreover, there is no controlled study of these complications, making it difficult to predict the extent and duration of speech changes or dysphagia. These complications can be a significant problem for patients who are actively engaged in social activities, and can be a major factor in avoiding BTX

treatment, especially for vocal professionals. In this study, all patients were informed of the possible effects and complications of BTX injections. As a result, only 5 out of 14 patients (11 patients with CG and 3 patients with IG) who did not respond to medication, agreed to the BTX treatment. Of the nine patients who refused BTX treatment, four could not accept the risk of worsening voices as they were vocal professionals, and five refused the BTX treatment because they had no vocal discomfort. Therefore, BTX may be the most effective option as the primary treatment for CG; however, considering the complications and symptoms, caution is needed during administration of BTX.

Conclusion

On comparison of the treatment results of CG and IG, patients with IG had a better response to PPI and SI combination therapy than patients with CG. Patients who do not respond to the initial combination medical therapy can expect good results from BTX treatment.

Conflict of Interests

The authors declare that there is no conflict of interests.

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