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# Vocal Process Granulomas: A Systematic Review of Treatment

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## Abstract

**Objectives:** Vocal process granulomas (VPGs) are benign laryngeal lesions with controversial treatment and a tendency to recur. There are several treatment options with unpredictable results, high recurrence rates, and disappointing long-term outcome. The aims of this article are to focus on evidence-based current treatment strategies for primary lesions and recurrences.

**Data Sources:** The data came from a systematic review of the literature.

**Methods:** Main outcome measures were recurrence rate, reduction, and/or complete resolution. Inclusion criteria included English literature, randomized and nonrandomized trials, prospective and retrospective studies, and primary and recurrent cases. Exclusion criteria included case reports, teaching reviews, and papers not focusing on treatment.

**Results:** The time frame of the included studies was from 1997 to 2012. There are 6 different treatment options (single or combined) for VPG. Antireflux medication is the mainstay treatment and when combined with lifestyle changes and voice therapy results in the lowest recurrence rate. “Bloodless” in-office or in-theater laser techniques appear to have lower recurrence rates when compared to traditional cold steel microlaryngoscopy techniques, especially for recurrences.

**Conclusions:** There is level 2A evidence that antireflux treatment is the main treatment strategy for vocal process granulomas with surgery reserved only for failures of medical treatment or airway obstruction or when diagnosis is in doubt.

## Keywords

vocal process granulomas, benign, lesions, larynx, gastroesophageal reflux, antireflux treatment, laser, proton pump inhibitors, speech therapy, recurrence, resolution

Management of vocal process granulomas (VPGs) remains a controversial topic for the laryngologist and head neck surgeon. Their etiology varies, treatment is difficult, and there is a high recurrence rate. They were first described as “contact ulcers” in 1928 by Chevalier Jackson,<sup>1</sup> who reported a superficial ulceration along the posterior aspect of the larynx.<sup>2</sup> At the time their etiology was thought to be voice abuse. Further application of endotracheal anesthesia led to a theory that VPGs can be a result of trauma secondary to prolonged intubation.<sup>3</sup> Since then, several other factors have been implicated in their etiology including voice abuse and gastroesophageal reflux disease (GERD).<sup>3-6</sup> Although these lesions are rare, recurrence rates of up to 90% have proven their management to be challenging.<sup>4</sup> The aims of this article are to focus on evidence-based current treatment strategies (primary and/or adjuvant) for primary VPGs and recurrences.

## Methods

A PubMed, MEDLINE, Embase, CINAHL, and Cochrane search was performed using the following keywords: vocal process granulomas, benign, lesions, larynx, gastroesophageal reflux, antireflux treatment, laser, proton pump inhibitors, speech therapy, recurrence, and resolution. References from the relevant articles were also searched. We included English literature, randomized and nonrandomized trials, prospective and retrospective studies, and primary and

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recurrent cases. We excluded case reports, teaching reviews, and articles not focusing on treatment of VPGs.

## Results

We identified 8 nonrandomized studies and 11 retrospective studies from 1997 to 2012. We included studies from primary and recurrent cases of VPG. Details of previous treatment in refractory studies are outlined in Table 1.<sup>7-24</sup> The 3 most common treatment options are antireflux therapy, mostly proton pump inhibitors (PPIs), speech and language therapy (SALT), and steroids. Surgical excision is usually reserved for refractory or recurrent cases. It is only used as first line treatment if there is diagnostic uncertainty or airway compromise. The majority of these studies are a retrospective look at medical records to ascertain the success of certain treatment modalities or treatment protocols. These studies dealt with a combination of the treatment options listed above, which made it difficult to assess the efficacy of each single treatment option individually. This reason together with selection bias, blinding of the results, and lack of common outcome measures were some of the problems preventing a formal meta-analysis.

### Antireflux Therapy

The majority of studies look at the use of antireflux therapy in combination with SALT and inhaled steroids. Only de Lima Pontes et al<sup>23</sup> retrospectively identified a small cohort of patients in which antireflux therapy was given in isolation. Patients received omeprazole and domperidone, of which 69% had resolution of their granuloma. Four studies<sup>3,11,19,21</sup> were identified in which PPIs were used in conjunction with either SALT or voice rest. The study by de Lima Pontes et al<sup>23</sup> found a combination of SALT and PPI to have a 100% resolution, but this a small study in which only 1 received concurrent PPI.

The remaining studies had resolution rates varying from 71% to 91%. The study by Carroll et al<sup>11</sup> is likely to most accurately reflect the efficacy of this particular dual treatment as nearly all the patients received both PPI and SALT (90%) with the remaining 2 patients receiving PPI alone. Havas et al<sup>19</sup> used a stepwise treatment protocol where all patients received SALT and only received antireflux therapy if GERD was present. The study identified that 76% of granulomas in their cohort were caused by GERD. Of these GERD patients 4 out of 42 patients failed to respond to maximum medical management. These 4 underwent fundoplication with subsequent resolution of their granulomas. Wani<sup>21</sup> et al treated all their patients with antireflux therapy with 52% of them also receiving SALT.

Patients on other combination treatments were also retrospectively identified in the studies by Hillel et al<sup>10</sup> and Lemos et al<sup>16</sup>, and the results are shown in Table 1. Lemos et al<sup>16</sup> yielded results with low resolution rates despite triple

treatment with PPI, inhaled steroids and voice therapy. The short follow-up time of 2 to 4 months may account for this finding.

### Speech and Language Therapy (SALT)

Three studies were identified in which SALT was the predominant treatment.<sup>6,22,23</sup> In both the studies by Ylitalo et al<sup>18,22</sup> a small proportion of the patients were also given antireflux therapy. Their studies yielded resolution rates of 53% and 58% but state that results may not be attributed as a whole to voice therapy.

As part of the study by de Lima Pontes<sup>23</sup> et al 8 patients were identified who received SALT; 7 of them had resolution of their granuloma (87.5%). These patients received targeted therapy as their granulomas were as a result of voice abuse and may account for the higher resolution rates found as compared to the Ylitalo et al studies.

### Steroids

Where steroids have been used in conjunction with other treatment modalities these have been discussed in the previous sections. There was only 1 study that was identified in which steroid treatment was given in isolation.<sup>7</sup> Chi-Te et al<sup>7</sup> administered monthly intralesional steroid injections for refractory granulomas. They achieved complete remission at 6 months in 60% of patients with at least 76% size reduction in the remaining patients.

### Botulinum Toxin

Botulinum toxin (BOTOX) was used in 6 of the 17 studies<sup>14,16,20,21,23,25</sup> and was reserved only for refractory granulomas. The article by Nasri et al<sup>25</sup> is the exception to this, as half their patients were given BOTOX injections as initial treatment. In the 3 studies<sup>14,20,25</sup> in which BOTOX was given to all patients, resolutions rates were 100%. However only Damrose et al<sup>14</sup> contained a cohort of patients in which BOTOX was given in isolation. In the other 2 studies concomitant therapy was given. In 3 other studies<sup>16,21,23</sup> BOTOX was used in a small percentage of their patients with "good effect" where initial treatment options had failed.

### Microlaryngeal Surgery

The majority of studies use conventional cold steel excision, carbon dioxide (CO<sub>2</sub>) laser ablation or potassium titanyl phosphate (KTP) laser ablation. It was not always possible to identify which approach was taken with some studies using more than 1 surgical technique. Where multiple surgical techniques were used it was not always possible to separate the outcomes for each technique. Surgery was predominantly reserved for those patients in whom initial

**Table 1.** Studies Focusing on Etiology, Types of Treatment, Reduction in Size, and/or Resolution and Recurrence Rates for Primary and Recurrent Vocal Process Granulomas.

REF	NoP	Study type	Etiology	Refractory VPG (previous treatment)	Tx length	Type(s) of treatment	Outcome	Rec. rate (%)	FU
Chi-Te <sup>7</sup>	10	NRT	Multifactorial NS	Yes	1-3 m	ILS	>90% reduction in size 100% asymptomatic	0	6 m
Sun <sup>8</sup>	16	NRT	External trauma/ intubation	Yes	1-3 m	Zinc sulphate TDS	100% resolution	0	12 m
Song <sup>9</sup>	21	RP	29% GERD 24% voice abuse 5% intubation 42% unknown	Yes	2-3 m	CO2 LA + radiotherapy CO2 LA without radiotherapy Both groups had 2 w voice rest postop	100% resolution 17% resolution	0 83	36-72 m 2 w-3 m
Hillel <sup>10</sup>	47 <sup>a</sup>	RP	35% intubation 28% vocal abuse 37% unknown	Yes	1-21 m	Inhaled triamcinolone + PPI +34% SALT +6% MLS	69% resolution 22% reduction in size 0% resolution	6 100	1-21 m
Carroll <sup>11</sup>	34	RP	53% GLI 26% intubation 26% unknown	No	6 m	PPI ± SALT (62%)	71% resolution 27% improved/ asymptomatic 7% persistent	0	2-19 m
					12 m	MLS ± BOTOX, ILS, VFIA (38%) Patients received PPI ± SALT as part of their treatment course	77% resolution 15% improved/ asymptomatic 8% persistent	46	4-23 m
Wang <sup>12</sup>	53	NRT	34% GERD 28% intubation 38% unknown	No	8 m	"Watch and wait"	82% resolution	2	NS
Lin <sup>13</sup>	12	RP	100% Intubation	No	N/A	KTP LA 75% patients also had PPI, SALT, Abx, or steroid therapy either alone or in combination	100% resolution	0	14-43 m
Damrose <sup>14</sup>	7	RP	86% URTI 29% voice abuse 14% GERD	Yes	2 w-2 m	BOTOX	100% resolution	0	12-32 m
Sulica <sup>15</sup>	35	RP	37% GERD 26% intubation 14% voice abuse 23% unknown	No	NS	PPI OD + InhS + SALT + 49% CO2 LA + 11% BOTOX Surgery performed in cases where VPG did not resolve	49% resolution 89% resolution 100% resolution	16	3-55 m
Lemos <sup>16</sup>	27	NRT	Multifactorial NS	No	NS	Fiberoptic laryngeal surgery (up to 3 repeated procedures) +7% PPI postoperatively	100% resolution	37 after first FLS 0 after third FLS	6-108 m
Hirano <sup>17</sup>	19	NRT	Nonintubation	No	1-15 m	Voice therapy +5% Cimet +25% AA	53% immediate resolution 84% resolution at 9 years	5	60-228 m
Ylitalo <sup>18</sup>	54 <sup>a</sup>	RP	76% GERD 33% voice abuse 23% intubation	No	NS	74% SALT ± H2A ± PPI ± fundoplication	91% resolution 8.9% required fundoplication	0	12 m
						26% MLS (16 out of 61 granulomas) + further SALT and antireflux therapy	50% resolution 88% resolution	50	
Havas <sup>19</sup>	8	NRT	Multifactorial NS	Yes	2 m	BOTOX + 88% PPI/H2A + SALT + 38% MLS	100% resolution	6	11-41 m
Orloff <sup>20</sup>	21	NRT	24% GERD 19% intubation 57% unknown	No	1-20 m	PPI OD 86%	78% resolution 22% size reduction	0	1-20 m
						H2A 14% 11 patients also had SALT + 6% MLS + 2/52 PPI OD + 11% BOTOX	100% resolution 50% resolution	50	2 years NS

(continued)

Table I. (continued)

REF	NoP	Study type	Etiology	Refractory VPG (previous treatment)	Tx length	Type(s) of treatment	Outcome	Rec. rate (%)	FU
Wani <sup>21</sup>	123	RP	Nonintubation	Yes (29% prior MLS)	NS	Surgery MLS 27% (31) CO2 LA 2% (2)	8% resolution	92	18 m
						NS MLS followed by SALT 21% SALT alone 53% Voice rest 24% Among these groups 16 patients given AA and 3 given PPI	50% resolution  34% resolution		
Ylitalo <sup>22</sup>	11	RP	23% intubation	No	NS	67% MLS (8)	100% resolution	0	NS
						33% SALT + PPI	100% resolution	0	
						PPI + domperidone + 19% MLS	69% resolution	6.3	
						44% SALT	66% resolution	33	
de Lima Pontes <sup>23</sup>	6	NRT	Multifactorial NS	Yes (50%)	2-8 m	56% MLS (10)	88% resolution	12.5	5-24 m
						BOTOX	50% resolution	50	
Al-Dousary <sup>24</sup>	41	RP	Multifactorial NS	No	23 m	MLS (8)	100% resolution	63	6 m
						+ PPI, domperidone, SALT + 38% BOTOX	25% resolution	100	
							100% resolution	0	
							First BOTOX injection	0	
							83% resolution		
							Second BOTOX injection		
							100% resolution		
							100% resolution		
							12% resolution	87	

Abbreviations: AA, aluminum alginate; Abx, antibiotics; BOTOX, botulinum toxin; Cimet, cimetidine; CO2, carbon dioxide; FLS, fiberoptic laryngeal surgery; FU, follow-up; GERD, gastroesophageal reflux disease; GLI, glottic insufficiency; H2A, H2 antagonist; ILS, intralesional steroid injection; KTP, potassium titanyl phosphate; LA, laser ablation; MLS, microlaryngeal surgery; MVFG, membranous vocal fold granuloma; NoP, number of patients; NRT, nonrandomized trial; NS, not specified; OD/BD, once a day/twice a day; PPI, proton pump inhibitors; REF, reference; RP, retrospective study; SALT, speech and language therapy; TDS, three times daily; Tx, treatment; URTI, upper respiratory tract infection; VFIA, vocal fold injection augmentation; VPG, vocal process granuloma.

<sup>24</sup>Number of granulomas, not number of patient.

medical management had failed. In some studies patients continued with medical management postoperatively, which makes some results difficult to interpret.

Carroll et al<sup>11</sup> divided their cohort of patients into surgically and conservatively managed. Of the surgically managed patients all were removed via cold knife excision. However some patients were also treated with additional measures including fibrin glue, BOTOX and vocal fold injection augmentation. Six patients could be identified as receiving surgical excision without the aforementioned procedures, for which there was 67% recurrence between 4 and 23 months.

Havas et al<sup>19</sup> used a treatment protocol where patients were initially treated with either antireflux therapy or voice therapy depending on pathology. Surgery was considered only after failure of initial medical treatment. Granulomas were removed by either cold knife excision or CO2 laser ablation. In all 16 patients underwent surgical excision with 50% resolution after 12 months.

The primary objective of the study by Ylitalo et al<sup>6</sup> was to assess the efficacy of voice therapy. However, the study also contains data on a cohort of patients who received surgery prior to receiving voice therapy. A third of the patients

in this study underwent surgery prior to voice therapy. Recurrence was reported as 92%, with a mean recurrence time after operation of 5 months.

In the study by de Lima Pontes et al<sup>23</sup> surgical excision was included in 3 of the treatment groups. There were a total of 26 patients that received surgery as first line treatment with 62% resolution and 38% recurrence. The exact surgical approach was not specified in this study, but the article states that all patients were given steroid injections into the vocal process prior to excision.

Hirano et al<sup>17</sup> report 37% resolution after a single surgical procedure and 100% after 3 procedures. The study reports that there were no recurrences in the follow-up periods from 6 months to 8 years. All procedures were done "in office" under local anesthetic with patients receiving forceps excision, forceps excision with vocal cord steroid injection, or KTP laser ablation. Two patients with a history of reflux received antireflux therapy postoperatively.

Song et al<sup>9</sup> looked at whether results with CO2 laser ablation could be improved with the addition of postoperative radiotherapy. All patients also received 3 days of postoperative antibiotics and 2 weeks of voice rest. They were able to compare results with and without radiotherapy as 6

of the patients refused radiotherapy. In those that received CO2 laser ablation alone there was 17% resolution. Those that also received radiotherapy all had resolution of their granuloma with no recurrence with follow-up that ranged between 3 and 6 years.

Lin et al<sup>13</sup> retrospectively reviewed 12 patients who underwent KTP laser ablation for postintubation granulomas. Most patients had also received antireflux, voice, and steroid therapy. They reported 100% resolution with no recurrence after 14 months.

Lemos et al<sup>16</sup> used CO2 laser ablation for patients in which there was failure of initial medical management. They report an 89% resolution with all patients continuing to receive medical therapy postoperatively.

Studies in which cold steel excision was the predominant treatment yielded resolution rates between 8% and 67%.<sup>11,17,19,23</sup> Comparing this to studies in which laser ablation was the predominant surgical technique, the resolution rates ranged between 17% and 100%.<sup>9,13,16</sup>

## Discussion

Antireflux therapy plays a significant role in the treatment of VPGs. Reflux is seen in 30% to 76% of cases of VPG.<sup>19</sup> The diagnosis of reflux related granulomas can be difficult with several studies treating patients empirically with anti-reflux treatment based on clinical findings on history and examination rather than pH metry.<sup>11,21,23</sup>

Antireflux therapy includes lifestyle measures, pharmacological treatment, and fundoplication surgery. The most common antireflux medications used for the treatment of VPGs are PPIs. Histamine antagonists and domperidone are also used. The study by Wani et al<sup>21</sup> suggests that omeprazole may be “better” for the treatment of VPGs than ranitidine. However these conclusions were based on the observation of only 4 patients. These patients took ranitidine instead of omeprazole, resulting in a 33% resolution rate as compared to 91% in the patients that took omeprazole.

Antireflux therapy is usually used in conjunction with voice therapy, which includes vocal hygiene and relaxation techniques. The addition of this voice therapy appears to increase the efficacy of treatment giving better resolution rates. De Lima Pontes et al<sup>23</sup> studied the effect of PPIs alone with a 69% resolution rate. In comparison, the studies that combined antireflux with voice therapy resulted in resolution rates of 71% to 91%.<sup>11,19,21</sup>

It is not clear whether the efficacy of treatment increases when antireflux treatment is targeted specifically toward proven GERD. This is seen when comparing the results of the studies by Wani et al and Havas et al. Both achieved a resolution rate of 91%, with Havas et al<sup>19</sup> treating only those with proven GERD and Wani et al<sup>21</sup> treating all VPGs patients with PPIs, although only 24% of their patients had an established diagnosis of GERD.

Intralesional steroids have been used to good effect with a 60% resolution rate following monthly injections.<sup>7</sup> Inhaled steroids, specifically triamcinolone has been recorded in the literature.<sup>10</sup> The evidence for it is scant, although the concept of reducing inflammation topically in a condition which is of inflammatory origin seems sound enough. In the studies where it has been utilized it has never been applied as a sole treatment, and when combined with antireflux therapy, has never been compared to antireflux therapy alone.<sup>10,16</sup> When combined with antireflux therapy resolution of VPG has been reported as 70%.<sup>10</sup>

Ylitalo et al produced 2 important studies looking at the effect of voice therapy on VPGs. In their earlier study<sup>18</sup> the authors state that “there is a long term healing process going on which has its own time frame.” This is to account for the long delay between healing and the conclusion of voice therapy. They make no definitive conclusions as to whether voice therapy contributed to the resolution rates found of 53% and 58%, with their later study<sup>22</sup> stating that “change in vocal behavior may create better circumstances for the healing process.”

The study by Wang et al<sup>12</sup> found that without any intervention a resolution rate of 83% could be achieved with mean remission times of 30 to 31 weeks. The study concludes that, although remission can be achieved without any treatment, the remission rates are longer than if treatment is given. This correlates with the above conclusions made by the studies by Ylitalo et al.<sup>18,22</sup>

In contrast, de Lima Pontes et al<sup>23</sup> had a greater resolution rate of 87.5%. The patients included in the above study<sup>18</sup> received targeted therapy as their granulomas were deemed to be a result of voice abuse. This targeted therapy may account for the higher resolution rates. However, this study contained only 8 patients, whereas Ylitalo et al had much larger cohorts.

There have been several studies citing Botulinum A toxin injection as a useful adjunct for the treatment of VPGs and is usually given for refractory VPGs.<sup>11,14,15,19,20,23</sup> The aim of BOTOX is to induce a chemical paralysis reducing the adduction trauma and allowing the mucosa of the vocal fold to regenerate. Unfortunately injecting the vocal cords results in hoarseness or breathiness or both until the toxin degrades, which must be weighed against benefits of the procedure.<sup>14</sup> In 1 study in which all patients received BOTOX there was a 100% resolution.<sup>14,15,20,23</sup> However these studies contained a very small number of patients with the largest of these studies consisting of 8 patients.<sup>20</sup>

The use of surgery for VPGs remains controversial due to recurrence rates postoperatively. It is indicated in patients who fail to respond to medical treatment, those who present with airway obstruction and of course when biopsy is required to exclude malignancy. Cold steel excision has been superseded by laser excision due to its accuracy, decreased recurrence rates and tissue damage. Various laser types have been

used in the treatment of granulomas including KTP, CO<sub>2</sub>, and pulsed dyed laser (PDL). Many of these can be used in the office in awake unsedated patients avoiding the risks of a general anesthetic and the complications of a rigid endoscopy. KTP laser has been shown to reduce lesion size by 22%,<sup>27</sup> whereas even better results were achieved in postintubation granulomas with a disease free period of at least 14 months.<sup>13</sup> Success was greater with other lesions of the larynx. KTP energy penetrates the epithelium without damaging it, due to the fragile nature of the mucoepithelium of the posterior larynx; this property is very appealing for laryngeal surgery. CO<sub>2</sub> laser has become more popular recently due to its advantages of decreased thermal damage to tissues and precise cutting. Koufman<sup>5</sup> presented a large series of 443 patients undergoing laser laryngeal surgery for various laryngeal pathologies including laryngeal papilloma. He used 3 laser types thulium: yttrium-aluminum-garnet, PDL, and CO<sub>2</sub> laser. All procedures were performed without sedation in the office setting. Lasers used in an office-based setting have been shown to be very cost-effective and safe.<sup>28</sup>

### Managing the Refractory VPG

Although there are many therapeutic strategies available to tackle VPGs, the most significant management dilemma is that of recurrence. Following treatment, recurrence most commonly recurs within the first 6 weeks.<sup>29</sup> Recurrence rates can be difficult to interpret with no clear definition of what constitutes recurrence and varying follow-up times ranging from 12 months to 8 years. Despite this it is clear that the recurrence rates following surgery for VPG can be considerably high (up to 92%).<sup>13,18</sup> Surgical excision recurrence rates are 4- to 5-fold those following medical treatment.<sup>19,23</sup> It can be argued that the recurrence rate increases with increasing follow-up time and, although this is likely to be true to some extent, there does not appear to be a direct correlation. Ylitalo et al<sup>18</sup> demonstrated a recurrence rate of 92% after a median follow-up of 5 months, whereas Hirano et al<sup>17</sup> found no recurrence with some patients being followed up for 8 years. It is possible that recurrence rates are affected by the surgical method used and the underlying etiology. Results appear to show that laser ablation may be superior to traditional cold steel excision with marginally better recurrence rates.<sup>9,13,16</sup> Song et al<sup>9</sup> have demonstrated that recurrence rates can be considerably improved by the addition of postoperative radiotherapy. However the long-term consequence of this is not known with the concern that this type of "overtreatment" for a "stubborn" but nevertheless benign problem can damage normal tissues and possibly induce malignancy. Medical treatment with lifestyle changes, voice therapy, and antireflux medication results in the lowest recurrence rate.<sup>16,19,30</sup> As there were no reported recurrences in the studies that used BOTOX for the majority of their patients,<sup>14,20,25</sup> it appears that it may be helpful

for cases of refractory VPG. It is also important when response is poor, to ensure the correct diagnosis backed up with histology is made.

### Conclusions

There is level 2A evidence that aggressive and prolonged antireflux treatment in isolation or combined with voice therapy are the main treatment strategy for VPGs with the lower recurrence rates. Surgery and especially laser techniques with or without injections are reserved for failures of medical treatment or airway obstruction or when diagnosis is in doubt. There is a need for randomized controlled trials especially for the cases of refractory VPGs.

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