Effect of the 532nm Pulsed KTP Laser in the Treatment of Reinke’s Edema

Michael J. Pitman, MD; Amy Lebowitz-Cooper, MS, CCC-SLP; Chodrin Iacob, MD; Meilin Tan, MD

Objectives/Hypothesis: To evaluate the effect and safety of the 532nm Pulsed Potassium-Titanyl-Phosphate (KTP) laser in the office-based treatment of patients with Reinke’s edema using objective and subjective scaled outcome measures.

Study Design: Case Series.

Setting: Tertiary hospital center.

Subjects: Seven adult females undergoing in-office KTP laser treatment for Reinke’s edema.

Methods: Participants were studied pre- and posttreatment. Vocal function was evaluated by objective aerodynamic and acoustic analysis. Subjective changes were evaluated using the GRBAS scale, Voice Handicap Index, and videostroboscopy. Histologic effects of the laser were investigated by comparing one patient treated with laser one year prior to excision, one treated with laser just prior to excision, and one control patient who underwent excision without prior laser treatment.

Results: At an average postoperative follow up of 17.8 weeks (range 5–78), maximum phonation time trended toward improvement. The median VHI score decreased from 37 to 26 (p = 0.150). There was a reduction in each component of the GRBAS scoring and the median fundamental frequency increased from 162 to 186 (p = 0.625). Stroboscopic findings demonstrated an intact posttreatment mucosal wave. Histologic comparison of the tissue effects of laser in three patients demonstrated changes in vocal fold vascularity but no acute or long-term damage to the overlying epithelium.

Conclusion: Objective and subjective scaled measures suggest that treatment of Reinke’s edema in the office with a 532nm KTP laser may result in improved voice. It appears safe with histologic preservation of the vocal fold vibratory epithelium and persistence of mucosal wave.

Key Words: Vocal Folds, vocal cords, Reinke’s edema, polypoid degeneration, KTP laser, Potassium, Titanyl Phosphate laser, dysphonia.

Level of Evidence: 4


INTRODUCTION

Reinke’s edema is a benign laryngeal disease involving diffuse polypoid degeneration of the vocal folds, precipitated most commonly by chronic tobacco use, but also by vocal abuse and laryngopharyngeal reflux. It manifests clinically with a rough vocal quality and lowered fundamental frequency.

Although Reinke’s edema is a benign disease, intervention is often indicated to improve voice quality and laryngeal function. Treatment begins with elimination of smoking, as well as addressing factors such as laryngopharyngeal reflux, which may exacerbate the dysphonia. Short-term voice therapy is appropriate to introduce optimal vocal behavior and reduce vocal abuse. Standard surgical intervention entails a microflap elevation, with removal of the polypoid degeneration and subsequent redraping of trimmed epithelium.1–2 Recently, studies have reported safe in-office treatment of laryngeal lesions with both the 585nm Pulse Dye (PDL) and the 532nm KTP in-office photoangiolytic lasers. Two of these studies reported safely treating Reinke’s edema with a photoangiolytic laser, but a quantitative evaluation of the benefits was not performed.3–4

We present our case series of seven patients with clinically diagnosed Reinke’s edema who were treated with a 532nm KTP laser. Their voice improvement was subjectively and objectively evaluated before and after treatment. Additionally, we compared the pathologic effect of laser treatment in two cases to the histologic findings in a patient who had not been treated with laser.

MATERIALS AND METHODS

Patients

In the study period between 2008 and 2009, seven patients identified with Reinke’s edema were enrolled, treated, and evaluated. Inclusion criteria were as follows: diagnosis of bilateral Reinke’s edema by primary investigator (MP), men and women ages 18–70, refused or failed a trial of conservative medical therapy and voice therapy, defined by lack of subjective
improvement in voice quality. All patients, were treated with twice a day proton-pump inhibitors for at least 2 months pre-treatment and posttreatment, and all were either Grade II or Grade III in severity. Exclusion criteria included unstable psychiatric disorder, inability to comply with the study protocol, pregnancy or lactation, lack of phone number or mailing address, or plans to change these within a 4-month period from time of treatment.

**Evaluation**

Patients underwent a full head and neck examination and formal videostroboscopy demonstrating bilateral Reinke's edema, and laryngeal function testing. Subjectively, the voice was evaluated using the Voice Handicap Index (VHI) and the GRBAS scales. The VHI was administered immediately prior to the laser procedure, as well as at 6 weeks postprocedure. Two trained laryngologists and a speech-language pathologist rated the recorded preprocedure and postprocedure voice samples according to the GRBAS scale. Evaluators were blinded in all cases with respect to subject identity and time of recording. For each recording, the mean of the three independent ratings for each scaling dimension constituted a final summary score. Interrater differences were evaluated across all samples and determined to be statistically insignificant (all p values > 0.0500). The pretreatment and posttreatment averages of GRBAS scores from each rater were then compared. Laryngeal functioning was assessed by several acoustic and physiologic measures, at the same time points as the subjective evaluations.

**Treatment**

In the office endoscopy suite, topical anesthesia including 0.25% phenylephrine, and 2% lidocaine was applied in the nasal cavity. For laryngeal anesthesia, 4% lidocaine was dripped on the larynx under direct visualization via a transnasal esophagoscope. After all standard laser precautions were taken, the laser fiber was passed through the transnasal esophagoscope. The vocal fold was treated with the KTP laser set at 25 watts, with a pulsed width of 15 milliseconds. As much of the area of the polypoid degeneration was treated as possible, including both the superior and inferior surfaces of the vocal fold. The end point was visualized blanching of the vocal fold at the time of laser treatment (Fig. 1). This is consistent with ischemia secondary to photoablation of vessels in the area. Initial patients enrolled in the study received bilateral but staged KTP laser treatment in order to prevent excessive glottic edema and airway compromise. The vocal fold with the greater amount of Reinke's edema was treated first. The opposite side, as well as any residual Reinke's edema on the initial side, was treated 1 month later. After treatment of several patients, the concern for edema with potential airway compromise was decreased and additional patients underwent an unstaged KTP laser treatment to bilateral vocal folds.

An average of 93.1 joules (range 44–141) was delivered at a given session. For the five patients who were staged, an average of 91 joules were delivered per side, compared to 103 joules delivered for the two patients who received KTP laser treatment to bilateral vocal folds in one setting. The patients who were staged underwent a total of two laser treatments, while those who were not staged underwent a single laser treatment. After each treatment, patients were placed on voice rest for 3 days and then asked to use their voice conservatively for the subsequent 2 weeks.

**Data Analysis**

Descriptive statistics were calculated and reported as mean plus standard deviation. Statistical analysis was performed using nonparametric tests (Wilcoxon signed rank test).

**Histologic Analysis**

One patient enrolled in the study opted to undergo direct suspension microlaryngoscopy with cold knife excision in the operating room 1 year after treatment with KTP laser because she desired greater improvement than the already significant improvement that she experienced from her laser treatment. Pathology slides from this excision were compared to those of another patient who had undergone application of KTP laser in the operating room minutes prior to direct suspension microlaryngoscopy with cold knife excision. Finally, both were compared to a patient with Reinke's edema who underwent cold knife excision without any prior KTP laser exposure.

**RESULTS**

Seven patients underwent staged or unstaged bilateral KTP laser treatments for Reinke's edema. All patients (100%) were female with a mean age of 51.8 years, and a range of 39–68. All patients (100%) had a positive tobacco history with at least a one-half pack-per-day smoking habit and treatment with maximal reflux therapy. Fifty-seven percent of the patients quit smoking, upon our counseling, prior to treatment. No complications were encountered.

Post-treatment videostroboscopy demonstrated an intact mucosal wave in all patients. In this pilot study, the median VHI score was found to decrease from 37 to 26 (Wilcoxon signed rank test: p=0.150). While five of...
the seven patients had a decrease in their VHI score, including one patient who had long term follow up of 18 months, two patients (patient #4 and patient #5) were noted to have an increase in their score.

There was a reduction in the GRBAS scoring with all components decreasing in the posttreatment evaluation when compared to the pretreatment evaluation. TABLE I demonstrates the pre- and posttreatment GRBAS scores, averaged among the three blinded examiners. The median Grade decreased from 2.0 to 1.5, Roughness decreased from 2.1 to 1.4, Breathiness decreased from 1.1 to 0.3, Asthenia decreased from 0.6 to 0.1, and Strain decreased from 1.8 to 1.2.

Objective voice testing was available for five of the seven patients in our cohort and demonstrated possible improvement in several parameters. Average Maximum Phonation Time increased from 4.522 seconds (± 0.59) to 7.53 seconds (± 4.5). Median fundamental frequency increased from 162 (range 96–199) to 186 (range 101–253) (Wilcoxon signed rank test: p = 0.625) This is reflected in Fig. 2. Changes in other parameters of acoustic/aerodynamic measures including Open Quotient, RAP%, noise:harmonic ratio, shimmer were statistically insignificant.

Figures 3–5 demonstrate histologic examination of three patients. Figure 3 demonstrates the vocal folds from one patient who underwent cold-knife excision in the operating room 1 year after treatment with KTP laser. This demonstrates small caliber blood vessels just under the intact epithelium with compromised vessel structure, an absence of damage to surrounding tissue, and less myxoid stroma and edema. This was compared to the pathology slides of another patient who had undergone application of KTP laser in the operating room minutes prior to direct suspension microlaryngoscopy with cold knife excision (Fig. 4). The vocal folds in this case demonstrated the typical myxoid and edematous changes characteristic of Reinke’s edema, with the addition of blood vessel wall degeneration and early clot formation secondary to the photoangiolytic laser effect. The epithelium and myxoid stroma was intact and unaltered. Both were compared to a patient with Reinke’s edema who underwent cold knife excision without any prior KTP laser exposure. Findings in this instance were benign epithelium with an expansion of Reinke’s space by myxoid and edematous changes. The blood vessels in the subepithelial area were normal with complete and well-formed walls (Fig. 5).

**DISCUSSION**

Reinke’s edema is a benign laryngeal disease involving diffuse polypoid degeneration of the vocal folds. It is well documented that the patients who are at risk for developing Reinke’s edema are chronic smokers. Vocal abuse and laryngopharyngeal reflux may also be precipitating factors. While it is a long-held belief that hypothyroidism may be a cause of Reinke’s edema, this is controversial. The condition clinically manifests with a rough vocal quality and decrease in fundamental frequency.

Anatomically, the body of the thyroarytenoid muscle is covered by the mucosal epithelium and the lamina propria. It is the superficial layer of the lamina propria that creates Reinke’s potential space. This space allows for decoupling of the mucosa so that it may oscillate with a significant amount of freedom from the underlying ligament and muscle. Chronic smoking, voice abuse, and laryngopharyngeal reflux result in edema, vascular congestion, and venous stasis within Reinke’s space. It is believed that chronic irritation alters the permeability of
capillary walls, leading to extravasation of fluid into Reinke’s space, making the vocal fold cover less stiff, more massive, and more compliant.\textsuperscript{9–10} Hence, the physiologic and anatomic properties of the tissues of the vocal fold are altered, with a negative impact on phonation.\textsuperscript{10}

Although Reinke’s Edema is a benign disease, intervention is often indicated to improve voice quality and laryngeal function. Treatment begins with elimination of etiologic factors, including smoking and laryngopharyngeal reflux. Short-term voice therapy is appropriate to introduce optimal vocal behavior and reduce vocal abuse. These measures may reduce the turgidity of the polyps, with a corresponding modest improvement in vocal functioning.

To date, there is no universally accepted single approach to the treatment of Reinke’s edema. Surgical treatment for Reinke’s edema and other benign vocal fold pathology historically consisted of vocal fold “stripping.” This de-epithelialization procedure, first described in 1964 by Kleinsasser,\textsuperscript{11} often resulted in poor outcome but was a common practice until the microarchitecture of the vocal fold was later elucidated.\textsuperscript{6} Understanding of the three-layer lamina propria that lies between the epithelium and the vocalis muscle spurned the microsurgical techniques that maximally preserve normal structures, including the all layers of the lamina propria and as much overlying epithelium as possible. In the case of Reinke’s edema, after the epithelial incision is made the polypoid tissue is either suctioned or dissected out, and the remaining epithelium is trimmed and redraped employing the microflap technique. This procedure allows for earlier and more optimal return of voice when compared to vocal fold stripping.\textsuperscript{9}

The use of lasers in laryngology is well documented. Carbon Dioxide (CO2) laser was reported for Reinke’s edema with improved acoustic result by Murray et al.\textsuperscript{12} In this study, it was shown that voice quality and pitch subjectively increased in eight subjects, and glottal configuration on stroboscopy showed improved closure. As the use of lasers in the larynx extended into office-based procedures, the use of photoangiolytic lasers for in-office treatment of Reinke’s edema followed suit with the 585nm PDL and the 532nm KTP laser.\textsuperscript{3–4,13} Both PDL and KTP lasers are photoangiolytic lasers that target the chromophore oxyhemoglobin and can be delivered via fiberoptic fibers in the office setting with only topical anesthesia. Though the wavelength and pulse duration of these lasers are different from each other, clinically
they are considered to be relatively interchangeable with similar, though not identical effect. While the histologic effect of photoangiolytic laser application on chick chorioallantoic membrane vessel coagulation and rupture has been well described, little is known about the effect of these lasers on the tissues of the human vocal fold.\textsuperscript{14} Previously, only tissue changes due to the use of a PDL in the treatment of dysplasia were examined, while studies evaluating the effect of the KTP laser on the human vocal fold, much less specifically on Reinke’s edema, have not been performed. Koufman and Wright reported a return to near-normal voice in four patients with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Hematoxylin and Eosin stains 20\times (4A) and 40\times (4B) magnification of Vocal Folds with Reinke’s Edema. KTP laser was applied in the Operating Room immediately prior to excision. H&E demonstrates unaltered myxoid and edematous change of Reinke’s space with an unaltered epithelium. Early clot formation is seen in the blood vessels and is evidence of blood vessel injury (black arrow). Periodic acid-Schiff (PAS) stain (4C) and Smooth Muscle Actin (SMA) stain (3D) shows mild degeneration of blood vessels wall (black arrow).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Hematoxylin and Eosin stains 10\times (5A) and 40\times (5B) magnification of Vocal Folds with Reinke’s Edema. No prior laser treatment was given. Benign epithelium covers an expansion of Reinke’s space. There is no change in blood vessels in the subepithelial area.}
\end{figure}
Reinke’s edema, within 8 weeks of PDL treatment. Similarly, Mouadeb and Belafsky demonstrated good qualitative effect of PDL on Reinke’s edema. While the photoangiolytic lasers have become an accepted treatment for patients with Reinke’s edema of the vocal folds, in the current literature there is minimal documentation of the subjective effect and no documentation of the objective effects of photoangiolytic laser treatment for this disorder.

In our cohort, both VHI and GRBAS scoring demonstrated subjective improvement at an average of 17.8 weeks (range 5–78) after a single KTP laser treatment to each vocal fold. The median VHI score was found to decrease from 37 to 26 (Wilcoxon signed rank test: p=0.150). This is largely a reflection of five of the seven patients, as two patients had an increase in their score. The VHI is a subjective rating which can be confounded by many different factors that are variable. Overall, the decrease in the median VHI score is promising and includes one patient (patient #6) who was evaluated at 18 months posttreatment with KTP laser, which suggests potential long-term benefit. It is possible with a larger sample size that a statistically significant change could become evident.

Objective acoustic and aerodynamic measurements demonstrated a trend toward improvement in maximum phonation time, which may be reflective of a decrease in the edema of Reinke’s space, allowing for improved efficiency of the glottis. Previous studies have demonstrated profound alterations in fundamental frequency after treatment of Reinke’s edema by other surgical methods, including vocal fold stripping, carbon dioxide laser excision, suctioning, or the microflap excision technique. The increase in fundamental frequency is a function of relieving the mass effect on the vocal folds. This significant elevation of fundamental frequency is crucial in that the chief complaint of patients with Reinke’s edema is generally their masculine voice. In this study, median fundamental frequency increased from 162 to 186. This frequency elevation would favorably change a voice perceived as masculine to a voice perceived as feminine. Further additional improvement in fundamental frequency has been noted in patients who underwent supplemental laser treatments if further improvement was desired and residual polypoid degeneration was noted.

Histologic analysis of three patients treated differently allowed an assessment of the tissue effect of the KTP laser on the human vocal fold with Reinke’s edema. The photoangiolytic properties of the 532 nm KTP laser worked immediately, with adverse effects on the blood vessels without any evidence of acute injury to the overlying epithelium or stroma through which the laser passes. These findings support the use of the KTP laser as a photoangiolytic laser targeting the vasculature without collateral damage to the surrounding tissue. Evaluation 1 year post-laser treatment shows persistent vessel wall injury, and a decrease in the myxoid and edematous stromal changes seen in Reinke’s edema. The pathophysiologic effect of a photoangiolytic laser on Reinke’s edema is unknown. It could be hypothesized that the laser effects are limited to the vasculature. It is possible that the reduction in stromal tissue and edema is due to a decrease in vasculature after coagulation or reduced permeability of the blood vessels within the superficial lamina propria. It is also possible that KTP laser exposure stimulates direct changes in the stroma, which slowly evolve posttreatment and hence are undetected here.

Most significantly, histologic analysis supports the safety of using the KTP laser on the vocal folds as there is no observed acute pathologic change to the vocal fold epithelium and no longterm complications. While treatment of the vocal folds with laser in the office could cause edema necessitating emergent airway management, we experienced no such complications in our series of patients. After initially approaching each patient with intention to stage their treatment, once it was observed that the treatment was safe, patients were treated bilaterally in one setting. A small number of patients, not included in this study, who had significant baseline dyspnea secondary to their Reinke’s edema, were pretreated with prednisone for 1 week and then treated bilaterally if the airway appeared to be adequate after resolution of some of the vocal fold edema. In this study, the treatment was well tolerated, offering patients an alternative to the traditional surgical methods requiring general anesthesia with potential for complications associated with microphonosurgery.

This pilot study was limited by its small number of subjects and relatively short follow-up time. Further studies with a larger cohort and longer longitudinal evaluation may be warranted. In addition, the optimal laser settings and joules to be delivered in the treatment of Reinke’s edema is unknown. Alternative settings and treatment with either more or less joules may have resulted in a different outcome. Despite this, the results evidenced both quantitative and qualitative vocal improvement when comparing preoperative and postoperative voice in patients with Reinke’s edema treated with 532nm KTP laser. Additionally, a review of the histology in two patients exposed to the 532 nm KTP photoangiolytic laser suggests that it is safe to use in Reinke’s edema with the acute effects limited to the vasculature and the chronic effects resulting in decreased myxoid stroma and edema without lasting untoward effects on surrounding tissues.

CONCLUSION
Treatment of bilateral Reinke’s edema with the 532nm KTP laser is promising. It results in quantitative and qualitative improvement of voice, including elevation of the fundamental after one treatment per vocal fold. Based on histological analysis, the laser can be considered safe with acute preservation of the vocal fold vibratory epithelium, as well as the presence of normal epithelium 1 year after treatment.

BIBLIOGRAPHY