Microlaryngoscopic and Office-Based Injection of Bevacizumab (Avastin) to Enhance 532-nm Pulsed KTP Laser Treatment of Glottal Papillomatosis

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Objectives: Photoangiolytic lasers effectively treat glottal papillomatosis, but do not reliably prevent recurrence. Therefore, sublesional injections of the antiangiogenic agent bevacizumab (Avastin) were given to assess the effect on disease recurrence and phonatory function.

Methods: A retrospective investigation was done in a pilot group of 10 adult patients with bilateral glottal papillomatosis who had prior angiolytic laser treatment with established patterns of recurrence. The patients underwent 5 bevacizumab injections (5 to 10 mg) into the diseased vocal folds along with 532-nm pulsed KTP laser photoangiolysis treatments 4 to 6 weeks apart. Their disease resolution was compared to findings from prior laser treatment alone, and objective measures of vocal function (acoustic, aerodynamic, Voice-Related Quality of Life survey) were obtained.

Results: All 10 patients had a greater than 90% reduction in recurrence. Four of the 10 had resolution. Four of the 10 have limited recurrent or persistent disease, receive injections of bevacizumab at 8- to 12-week intervals, and have not required laser treatment. Two of the 10 have ongoing periodic office-based KTP laser treatment along with bevacizumab injections. No patient has required microlaryngeal surgery with general anesthesia, and all 10 have had substantial improvement in vocal function.

Conclusions: This pilot investigation provides preliminary evidence that bevacizumab injections enhance photoangiolytic laser treatment of glottal papillomatosis while enhancing phonatory function. Coupling an antiangiogenesis agent with pulsed KTP laser photoangiolysis is conceptually promising, since the mechanisms of action are complementary.

Key Words: Avastin, bevacizumab, glottis, KTP laser, larynx, laser, papilloma, papillomatosis, recurrent respiratory papillomatosis, vocal cord, vocal fold, voice.

INTRODUCTION

Laryngeal recurrent respiratory papillomatosis (RRP) has been an omni-temporal clinical problem since the origin of laryngology as a specialty 150 years ago. A historical review of prior management of RRP is valuable to provide perspective for present and future treatment strategies. In the pre-laryngology era of the early 19th century (before 1857), deaths from RRP were illustrated in the postmortem assessment of those patients suffering from progressive airway obstruction (Fig 1). At that time, the only therapeutic intervention was tracheotomy, which was treacherous and not broadly available as an option. With the widespread adoption of mirror laryngoscopy in Europe and the United States in the 1860s, visually guided cold-instrument removal of papillomatosis lesions (Fig 2) became increasingly commonplace, as Hooper noted that “papilloma is the most frequent morbid growth found in the larynx” (see Appendix). The introduction of topical mucosal anesthesia with cocaine in 1884 advanced mirror-guided endoscopic techniques and allowed for the introduction of formalized direct laryngoscopy. However, in the 19th century, mirror-guided and direct laryngoscopic removal of papillomatosis was performed as an office-based procedure.

Direct laryngoscopic treatment was initiated in the office, but migrated to the operating room in the early 20th century because of the enhanced precision provided by improved instrumentation, along with personnel to assist with the procedures, including those responsible for administering anesthesia.

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Treatmenl of laryngeal papillomatosis in the first half of the 20th century primarily comprised cold-instrument removal, as well as ablation with caustic chemicals and/or electrical desiccation (Fig 3).\(^4,5\) In the latter 20th century, electrical desiccation was replaced with more precise carbon dioxide (CO\(_2\)) laser ablation,\(^13-15\) and cold instrumentation was enhanced by power-driven microdebriders.\(^16\)

In summary, surgical innovation for the endoscopic treatment of RRP of the larynx comprised interventions that would accelerate the speed and efficiency by which the mucosal disease could be removed in balance with the preservation of the delicate laryngeal soft tissue. Understandably, these goals were modulated by the severity of both airway and vocal dysfunction. After Anderson and Parrish\(^17,18\) conceived selective photothermolysis for the treatment of benign vascular malformations of the skin, subsequent pulsed angiolytic lasers were used to treat laryngeal papillomatosis. The fiber-based angiolytic lasers such as the 585-nm pulsed dye laser (PDL)\(^19,22\) and the 532-nm pulsed potassium titanyl phosphate (KTP) laser\(^23,25\) were more effective for treating laryngeal papillomatosis than was the CO\(_2\) laser, which had become the standard of care in a majority of institutions.

After performing a larger-scale investigation into the use of the 585-nm PDL for papillomatosis\(^22\) and dysplasia,\(^26,27\) we performed the first office-based angiolytic laser procedure by means of a flexible laryngoscope in November 2001.\(^12\) Remarkably, in 1995, Blitzer\(^28\) had performed a mechanically similar procedure with a novel CO\(_2\) laser fiber; however, that initiative did not progress because of difficulties
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After several hundred 585-nm PDL procedures, we abandoned this technology approximately 4 years ago for the substantially more precise and reliable solid-state 532-nm pulsed KTP laser. Among its advantages, the KTP laser provided significantly enhanced selective photoangiolyis due to the tunability of the pulse width. This greatly accelerated the speed and precision of procedures while maximally preserving the extremely delicate layered microstructure of the vocal folds. Furthermore, the KTP laser energy could be delivered on a laser fiber approximately 50% smaller than that of a PDL, and this improvement substantially enhanced the critically important suctioning capability required for effective office-based laser treatment of papillomatosis.

Because of the ease and success of office-based 532-nm pulsed KTP laser treatment of papillomatosis, more than 85% of our laryngeal papillomatosis procedures are done in the office, as is overwhelmingly our patients' preference. In fact, of he more than 50 patients whom we follow for RRP, very few have required ongoing microlaryngoscopic management with general anesthesia. However, cumulatively, there are more office-based procedures done than there would be if the patients were treated under general anesthesia, because there is only limited procedural time with topical anesthesia. Understandably, a short time window for local anesthesia requires that a limited volume of disease be present at each procedural encounter.

Patients and surgeons have preferred this model of more-frequent procedures over microlaryngoscopic care. When general anesthesia was the only option, it was commonplace for both patients and surgeons to employ watchful waiting until there was substantial symptom deterioration warranting surgical intervention. This waiting led to wide fluctuation in patient function. However, regardless of the surgical technique used to remove the papillomatosis neoplasms, no surgical intervention provided obvious long-term resolution of the disease. Therefore, we sought to employ an adjuvant medical management to diminish the severity and frequency of recurrence. Consequently, this would mitigate the impact of the increased frequency of the office-based procedures, which still required mucosal ablation of the epithelial disease. Given our observations of patients from other institutions who had sustained permanent severe hoarseness from loss of pliable phonatory mucosa subsequent to cidofovir injections, we sought a different pharmacologic prevention strategy in accordance with our angiolytic laser treatment philosophy.

In his candidate's thesis for the American Laryngological Association in 1882, Hooper perceptively noted, "The vascularity of the growth (papillomatosis) is perhaps the most important factor in determining the rapidity of its reappearance." One hundred years later, Folkman established that angiogenesis is a multistep process primarily initiated through vascular endothelial growth factor (VEGF). VEGF initiates a cascade of intracellular signal transduction pathways resulting in the formation of new vessels. Given the microcirculatory histology of RRP, there is evidence that VEGF plays an important angiogenic role in the pathogenesis of RRP.

Bevacizumab (Avastin) is a humanized monoclonal antibody that is known to inhibit angiogenic neoplastic growth by binding to VEGF before its attachment to its natural receptors. It has been used intravenously for a variety of metastatic malignant neoplasms of the lung, colon, kidney, ovary, and, recently, the head and neck. There have been substantial vascular and renal complications associated with these systemic treatment regimens, which are difficult to parse because of the nature of the host populations. Low-dose intravenous therapy is considered to be 5 to 7.5 mg/kg (approximately 350 to
Much lower doses of bevacizumab have also been used extensively since 2005 as a local injection in the eye to inhibit angiogenic processes from a variety of eye disorders and diseases such as macular degeneration. To date, there have been more than 650 reports on the ophthalmological use of Avastin to inhibit angiogenic processes. Of these, more than 350 were published since 2008. Large-scale reviews of intravitreal injections in more than 5,000 patients (many with substantial medical comorbidities) at doses from 1 to 2.5 mg did not demonstrate substantial systemic complications. 41, 42 An analysis of 5,228 patients reported an extremely low 0.21% incidence of adverse events. This included a wide spectrum of local and systemic complications, including blood pressure elevation, transient ischemic attacks, cerebrovascular accidents, and death. Recently, combined use of the KTP laser with local injection of 100 mg of bevacizumab was noted to be superior to KTP laser treatment alone in the treatment of epistaxis related to hereditary hemorrhagic telangiectasia. 43

Sublesional injection of an antiangiogenic drug such as bevacizumab at the time of an angiolytic laser removal of laryngeal papillomatosis is a clinically attractive model. Having been able to convert all of our laryngeal papillomatosis patients to office-based management, our next clinical goal was to diminish the number of laser procedures required to control the disease and/or discontinue the need for laser treatment entirely. Toward that end, similar to the ophthalmological initiatives, we initiated the off-label intraresional and sublesional injection of bevacizumab at the time of angiolytic treatment in a pilot group of patients.

MATERIALS AND METHODS

From an initial cohort of 53 patients with RRP, a retrospective investigation was done in a pilot group of 10 adult patients with recalcitrant glottal RRP who had prior angiolytic laser treatment with established patterns of recurrence. Three of the 10 presented with airway obstruction, and 7 of the 10 were being treated for vocal dysfunction associated with frequent disease recurrence. Subepithelial (within the superficial lamina propria) bevacizumab injections (5 to 10 mg) into diseased vocal folds were used along with pulsed KTP laser photothermolysis treatments 4 to 6 weeks apart until laser ablation was discontinued because it was not necessary to maintain optimal vocal function (Fig 4). The patients underwent an initial series of 5 bevacizumab injections of 5 to 10 mg (0.2 to 0.4 mL: 2.5 mg/0.1 mL); the subepithelial injection dose was related to the amount of scarring present from prior procedures in the subepithelial superficial lamina propria, and the treatment interval was based in part on practical considerations of patients' travel constraints. Disease assessment was quantified, similar to prior descriptions, 12 by comparing findings of office laryngoscopic examinations prior and subsequent to the use of bevacizumab.

Bevacizumab injections were done with a microfluorescent microscopy infusion needle (Endocraft LLC, Winter Park, Florida) in the operating room, along with use of the Universal Modular Glottiscope (Endocraft LLC). 45 The anatomic rationale and procedural technique have been detailed previously. 11 Office-based injections were given with the Ford system (Medtronic Inc., Minneapolis, Minnesota) with rigid telescopic guidance (KayPENTAX, Lincoln Park, New Jersey) or by Amin's transcervical technique with flexible laryngoscopic control (KayPENTAX). 48

The patients underwent standard voice assessments before and after the series of bevacizumab injections. These included videostroboscopy, completion of the Voice-Related Quality-of-Life survey (V-RQOL), 49 and objective acoustic and aerodynamic measures of vocal function. Because of its reliance on subjective judgments, observations from videostroboscopic recording were not used as formal data and are only included in the context of discussing the results of vocal function measures. The details of the protocol for obtaining acoustic and aerodynamic measures of vocal function have previously been described. 50 When possible, postinjection measures were compared descriptively with preinjection measures and with historical norms for individual patients.

RESULTS

In comparison to their prior glottal recurrence pattern with laser treatment alone, all 10 patients (20 vocal folds) had a more than 90% reduction in recurrence while maintaining or improving mucosal pliability. In addition, 7 of the 10 patients (14 of the 20 vocal folds) had complete clinical resolution of the disease. Of those 7 patients, 4 had clinical resolution, and 3 developed mild recurrence 8 to 10 weeks after the cessation of the bevacizumab injection. However, all 3 are being maintained with excellent function by use of office injections and without laser ablation. All 3 of the 10 patients who did not achieve clinical resolution after a series of 5 injections had presented with airway obstruction. Over time, 1 of the 3 demonstrated very limited epithelial disease
Fig 4. A) Bilateral recurrent respiratory papillomatosis in glottis of 40-year-old classical vocalist. He had undergone multiple 532-nm pulsed KTP angiolytic laser procedures, which preserved phonatory mucosal pliability but did not prevent disease recurrence. B) Same examination during adduction. C) Office-based injection of 7.5 mg of bevacizumab was given in subepithelial superficial lamina propria of right vocal fold. Infusion has visually displaced right-sided disease caudally. D) On same day, after bevacizumab injection, office-based 532-nm pulsed KTP photoangiolysis is done on disease bilaterally. Note white eschar in laser-treated regions and that 0.3-mm fiber (arrow) is in contact with exophytic lesion within anterior commissure region of left vocal fold. E) Laser procedures were discontinued after second injection. Patient subsequently underwent total of 3 more injections. It has been 6 months since last injection, and active disease is not seen. F) Same view as in E during adduction; there are substantial secretions noted in glottal introitus consistent with reflux history.

that warranted ongoing injections (see Figures on cover), but did not require a surgical ablative treatment of the phonatory mucosa. Therefore, 4 of the 10 cases are at present resolved, and 4 of the 10 patients have limited recurrent or persistent disease and are injected with bevacizumab at 8- to 12-week intervals, somewhat as in a dystonia model. Two of the 10 patients continue to receive office-based KTP laser treatment combined with bevacizumab injections. These 2 individuals had initially presented
with severe airway obstructive symptoms; 1 of them had a tracheotomy. In summary, no patient requires microlaryngeal surgery with general anesthesia, and only 2 of the 10 patients (4 of the 20 vocal folds) still require office-based laser treatment of vocal fold membranes. There were no systemic or local complications as a result of the bevacizumab injections.

In this pilot study, we utilized a subset of 4 primary voice assessment measures to evaluate the impact of the new treatment regimen on vocal function. The measures included the overall V-RQOL score, the average fundamental frequency during reading of a standard passage (Fo: vocal pitch), the noise-to-harmonics ratio during sustained vowels (NHR: voice quality), and the ratio between vocal sound pressure level and average subglottal air pressure during production of standard syllable strings (in decibels per centimeter of water: vocal efficiency).

Figure 5 shows results for the V-RQOL survey. On this scale, 0 indicates the lowest voice-related quality of life and 100 indicates the highest voice-related quality of life. Across all patients, the preinjection scores (7 patients) ranged from 28 to 60 and the postinjection scores (10 patients) ranged from 82 to 100. All 7 of the patients who completed the V-RQOL before and after treatment displayed dramatic increases in postinjection scores ranging from +30 to +95. Pretreatment scores were not available for patients F2 and F3 (who were initially assessed before we began using the V-RQOL) or for patient M2 (who presented with airway obstruction and was taken emergently to the operating room before any pretreatment voice assessment could be done).

For the remaining vocal function measures, there were no pretreatment voice assessment data for patients M1 and M2, because both were aphonie and 1 presented with a tracheotomy, and there were no posttreatment aerodynamic measures for M7 because of technical difficulties. Figure 6 displays the results for average Fo during the reading of a standard passage with female and male data assessed separately because of normal gender-based differences in vocal pitch (ie, the average female pitch being approximately 1 octave above the average male pitch). Patient F1 displayed an abnormally elevated Fo before treatment (249 Hz) that then fell to a lower-than-normal value after treatment (161 Hz). The Fo for patient F2 was within the normal range (204 Hz) before treatment, but it decreased to a lower-than-normal level after treatment (156 Hz). Patient F3 displayed an elevated Fo (259 Hz) before treatment, but a normal Fo (199 Hz) after treatment. Six of the 7 male patients had posttreatment Fo values that fell within or closely approximated the normal range. All 5 of the male patients who had Fo assessments before and after treatment showed improvements in posttreatment Fo values in the form of decreases that ranged from −3 Hz to −122 Hz. Only
patient M2 showed a significantly elevated post-treatment Fo value.

The results for the voice quality–related measure of NHR are shown in Fig 7. Nine of the 10 patients displayed posttreatment NHR values that fell within or closely approximated the normal range. Seven of the 8 patients who had NHR assessments before and after treatment showed improvement in posttreatment NHR values that ranged from -0.008 to -0.58, and 1 patient maintained the same normal NHR value before and after treatment.

Figure 8 shows results for the ratio of sound pressure level to subglottal air pressure (decibels per centimeter of water) during syllable production, which reflects vocal efficiency. Only 2 of the 9 patients who had posttreatment measures attained the normal threshold. However, all 7 of the patients who had assessments before and after treatment showed improvements in posttreatment vocal efficiency that ranged from +0.5 to +9.9.

DISCUSSION

The observations herein of local adjuvant injections of bevacizumab used to treat glottal RRP have provided a proof of concept that pharmacologic antiangiogenesis is efficacious. Because of the dramatic findings in this pilot group of patients and the suboptimal long-term results of clinical treatment strategies, along with the compelling morbidity associated with glottal RRP, we thought it was important to share this preliminary information before undertaking a larger-scale investigation.

Laryngeal papillomatosis has had a steady and consistent clinical influence on laryngology since the origin of our specialty, as is evident in early textbooks. This omniternal impact is unlike the influence of the majority of infectious airway diseases that dominated laryngological literature in the 19th century and unlike epithelial cancer, which has been a centerpiece of 20th-century academic investigation. There are few patients and surgeons who would not welcome a nonmorbid systemic medical treatment for laryngeal papillomatosis so that this disease could be relegated to historical significance, as were other once-common laryngeal diseases such as tuberculosis and diphtheria.

It is reasonable to expect that an effective systemic medical treatment will be available in the foreseeable future, given the interest in human papillomavirus vaccines. In anticipation of this likely advancement, a critical responsibility of laryngeal surgeons today is to treat patients with technologies that do not damage the laryngeal soft tissues with imprecise ablative treatment. Most importantly, great care must be given to preserve the delicate subepithelial superficial lamina propria, which is primarily responsible for the phonatory mucosal pliability necessary for normal vocal fold vibration. Remarkably,
these management principles were delineated by Hooper more than 125 years ago.

For the past 150 years, the primary treatment of laryngeal papillomatosis has remained a transoral, minimally invasive cytoreduction surgical treatment directed at managing symptoms of airway obstruction and vocal dysfunction. Systemic medical treatments such as interferon and indole-3-carbinol, as well as local injections of cidofovir, have had limited success and acceptance. Moreover, we have encountered a substantial number of patients who have sustained severe and permanent hoarseness from incurable stiffness of phonatory mucosa subsequent to local cidofovir injections. Remarkably, voice outcome data are generally omitted in cidofovir-related literature; however, vocal fold scarring and intractable hoarseness have been reported. This unpredictable and disabling voice outcome will continue to restrict the widespread use of cidofovir in papillomatosis patients in whom the airway is stable and phonatory dysfunction is the primary indication for surgery. In addition, there remains some concern about the potential carcinogenicity of cidofovir.

Given the voice problems observed with local injections of cidofovir, we proceeded very cautiously in the initial glottal administration of bevacizumab, although we were reasonably comfortable with the limited risk of systemic complications. The injection strategy we employed was commensurate with the ophthalmological model, for which there is an extensive literature on the off-label use of bevacizumab with minimal difficulties despite a predominantly elderly population. Although we employed doses that were approximately 5 to 10 times greater than that used for the eye, our doses were still less than one-fifteenth that of systemic intravenous cancer treatment.

The initial 2 patients who underwent local injections of bevacizumab had ominous chronic airway impairment despite repeated surgery and were compelled by the severity of their disease to try a novel treatment strategy. Initially, only one vocal fold was injected. After observing a dramatic diminishment of the pace of disease recurrence, along with substantial voice improvement, we treated the second vocal fold as well. However, it was difficult to assess the effect of the bevacizumab on the superficial lamina propria (phonatory mucosal pliability), because these patients had substantial prior surgery at other institutions.

The key patient who assisted us in initially assessing the effect of bevacizumab on phonatory mucosa was a classical singer (Fig 4) whose glottal papillomatosis had ended his career. We had performed his prior surgical procedures as microlaryngeal and office-based pulsed KTP laser interventions. Accordingly, there was confidence that his sublonsional superficial lamina propria was uninjured so that the effect of bevacizumab on mucosal pliability could be assessed. To mitigate the potential for permanent vocal dysfunction, we initially injected only the more-diseased vocal fold while we performed office-based pulsed KTP laser treatment of both vocal folds.

After observing the diminished recurrence of disease in the clinically worse vocal fold and the enhanced mucosal wave function, we used the treatment strategy bilaterally and subsequently with other adult patients. Before bevacizumab injections, this individual developed recurrence in 8 to 10 weeks despite KTP laser treatment. Since completing a series of bevacizumab injections, he has no clinical evidence of disease 6 months after his last injection and has not had a laser procedure in 10 months. Most remarkable, his singing is without restriction, comparable to his pre-disease state.

Encouraging and dramatic results were noted in all 10 patients; all have had greater than 90% improvement as compared with prior patterns of recurrence with KTP laser treatment alone. Four of the 10 have had resolution so that they no longer have discernible disease. Another 4 of the 10 have microscopic disease managed solely by office injections of bevacizumab at 8- to 12-week intervals. Only 2 of the 10 currently require ongoing glottal laser treatment, which is done solely in the office, and the recurrences are very limited as compared with prior recurrence patterns. Both of these patients initially presented with severe disease manifested by airway obstruction, and 1 of them had a tracheotomy.

The 10 cases reported herein illustrate that patterns of presentation and recurrence in patients with RRP comprise a wide spectrum. We have not noted that different surgical ablation technologies substantially alter recurrence patterns, apart from the fact that easier techniques often led to more complete removal. Effective surgical techniques primarily enable more comprehensive removal of clinically visible disease in a time-efficient fashion while preserving soft tissue and voice. Alternatively stated, we do not believe that any current surgical method that preserves the layered microstructure of the glottis results in a biological change in the papillomatosis-host relationship and/or the recurrence pattern. Accordingly, we expect that there will be a spectrum of responses to bevacizumab, with varied patterns of recurrence commensurate with the spectrum of disease presentation.
With regard to voice outcome, the patients displayed substantial improvements in posttreatment vocal function. This was reflected most clearly by the dramatic increases in patients’ self-assessments of their voice-related quality of life following the new treatment regimen (see V-RQOL results in Fig 5). Most patients also had posttreatment improvement in voice quality (see HNR results in Fig 7) and vocal efficiency, and a majority of patients actually achieved normal posttreatment NHR values. On the other hand, even though vocal efficiency improved, only 2 patients achieved normal levels (Fig 8). These results are in line with previous observations that patients with mild persistent phonatory deficits have the capability to adjust underlying aerodynamic parameters to achieve or approximate normal voice quality.61

Stroboscopic observations corroborated the objective vocal function test results. Improvements in voice quality (NHR) and vocal efficiency (decibels per centimeter of water) were reflected by posttreatment improvements in the amplitude and symmetry of vocal fold mucosal wave activity, and by more-complete glottal closure during phonatory vibratory cycles. The lowered posttreatment F0 values for the female patients were attributed to the vibratory mucosa’s being slightly enlarged (mass-loaded) and more pliable, as it appeared to be in the posttreatment stroboscopic examinations of these patients. Stroboscopic observations in the one male patient who displayed a significantly elevated posttreatment F0 value revealed a persistence of adynamic segments of vocal fold mucosa with reduced mucosal wave activity that accompanied the impression of a strained, high-pitched voice, undoubtedly the result of the initial surgical management for his disease.

Our goal in introducing bevacizumab as a pharmacologic modulating agent to treat RRP was to diminish the number of office-based laser interventions12,23 in which the glottal mucosa required ablation. We had previously established that microlaryngoscopic treatment of adult RRP could be mostly avoided, minimizing the morbidity of multiple general anesthetics.12,23 It is our belief that use of periodic office-based injections of a pharmacologic agent, similar to the model of using Botox for dystonia, has the greatest likelihood of preserving voices and the layered microstructure of vocal folds as we await the development of a curative vaccine.

The results and observations from this study are promising and warrant further investigation. It would be valuable to gain further insights such as clarifying the number of initial bevacizumab injections that optimally control the disease. What is the typical time after completion of a series of injections until there is visible recurrence, and subsequently, when does voice deterioration occur, thereby warranting papiloma cytoreduction to restore vocal quality? If limited disease is observed, can reinstitution of bevacizumab injections preclude the need for a laser intervention? Will some patients demonstrate long-term remission? Will repeated injections result in systemic complications (eg, hypertension and proteinuria), previously noted in higher-dose intravenous administration? Will there be a difference in response between children and adults? Will intravenous bevacizumab provide assistance to those adults and children with life-threatening airway obstruction or in the severest intrathoracic cases?

We are currently designing a multi-institutional, randomized prospective trial to examine these questions. If bevacizumab is conclusively determined to be effective, future pharmacologic strategies could slow the drug release in soft tissue. Alternatively, research efforts might identify more effective antiangiogenesis agents and/or modify the route of administration so that the drug is nebulized to be topically inhaled.62

CONCLUSIONS

This pilot study provides preliminary evidence that bevacizumab enhanced the photocoagulation laser treatment of glottal papillomatosis while maintaining the pliability of the phonatory mucosa. Larger patient cohorts and multi-institutional studies are warranted. Coupling an antiangiogenesis agent with 532-nm pulsed KTP laser photocoagulation is conceptually attractive and promising, since the mechanisms of action are complementary. This effort provides clinicians with a new avenue for investigating local injections of antiangiogenesis pharmacologic agents as a primary or adjuvant treatment for other mucosal diseases and for neoplasms of the aerodigestive and genitourinary systems, as well as skin.

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Hooper was keenly aware that the primary metrics of success for patients with laryngeal RRP are maintenance of voice quality and airway safety. "It means simply that the great rule in surgery, 'not to do harm,' applies with double force to operations about such a delicate and important organ as the larynx. It means that the best method by which they can be extirpated is that which offers the least violence, and runs the least danger of inflicting injury, to the vocal organs." These key principles resonate today with all surgeons who apply with double force to operations about such a delicate and important organ as the larynx. It means that the surgeon has no power to cure or even arrest these new formations. Hooper astutely acknowledged the concept of spontaneous evolution, but pointed out that there is "...no means of determining when this fortunate moment will arrive." He also stated that "...recurrence is probably much more frequent than the bare numerical growth found in the larynx..." and that "...how best to eradicate them and prevent their reappearance, is still far from satisfactory." He stated that "...recurrence is probably much more frequent than the bare numerical statements which we have at hand would lead us to suppose..." He also stated that "...the surgeon has no power to cure or even arrest these new formations." Hooper astutely acknowledged the concept of spontaneous evolution, but pointed out that there is "...no means of determining when this fortunate moment will arrive."

Hooper began the manuscript by reminding the reader that "...papilloma is the most frequent morbid formation..." and that "...how best to eradicate them and prevent their reappearance, is still far from satisfactory." He stated that "...recurrence is probably much more frequent than the bare numerical statements which we have at hand would lead us to suppose..." He also stated that "...the surgeon has no power to cure or even arrest these new formations." Hooper astutely acknowledged the concept of spontaneous evolution, but pointed out that there is "...no means of determining when this fortunate moment will arrive."

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manage RRP.

Hooper strongly advised maintenance of airway lumenal patency "...before the larynx has become occluded, necessitating tracheotomy, or else leading to the fatal results familiar to us in so many cases in the ante-laryngoscopic days, and handed down to us in Ehrmann’s classical monograph" (see Ehrmann¹). Hooper defied Lewin’s² position, which was to employ watchful waiting until the patient with RRP had airway symptoms severe enough to justify tracheotomy. It is important to understand that this was a bold position by Hooper, since Lewin² had published the first series of laryngoscopic lesion extirpations more than 2 decades earlier. However, Hooper was very practical and appropriately judged that serial laryngoscopic interventions to avoid emergency tracheotomy in patients with impending airway obstruction was the wiser treatment strategy. This surgical decision-making is correct today, as well, and would have been even more significant in the context of the difficulty of tracheotomy in the 19th century.³

Especially pertinent to our current manuscript and to Hooper’s skill and foresight as a clinician is his statement that "the interval which elapses between the removal and the recurrence of papillomata varies considerably." Yet he intuitively acknowledged the concept of angiogenesis in these benign neoplasms: "The vascularity of the growth is perhaps the most important factor in determining the rapidity of its reappearance."

Franklin Hooper graduated from Harvard Medical School in 1876. After receiving specialized training under Leopold Schrötter in Vienna, he returned to Boston to join Frederick Knight as the junior laryngologist at the Massachusetts General Hospital and Harvard Medical School. Inspired by his mentor, Frederick Knight,⁴ who was the third President of the ALA, Hooper was likely the first American laryngeal surgeon-scientist. He championed scientific mammalian investigations to enhance the understanding of human vocal fold paralysis and by doing so was a key pioneer in the development of experimental neurolaryngology more than a century ago.⁵-⁹ These internationally recognized investigations by Hooper elevated the ALA as an academic organization during its infancy. With tragic irony, he died of metastatic tongue carcinoma at the age of 42, despite attempts at surgery in the United States and then by the esteemed British head and neck surgeon Henry Butlin.¹⁰

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