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Original Article

Adjuvant Intralesional Bevacizumab in Pediatric and Adult Populations With Recurrent Respiratory Papillomatosis: A Systematic Review

Ursula E. Gately, BS [1], Nan Zhang, MS [2], William E. Karle, MD [1], and David G. Lott, MD [1]

Objective: Recurrent respiratory papillomatosis (RRP) is a rare disease of the airway for which there is no known cure. Treatment involves the surgical removal or destruction of these lesions. There has been a long-standing debate over the effectiveness of the adjuvant intralesional injection of the immune modifying agent bevacizumab. This study is a systematic review investigating the effect of adjuvant intralesional bevacizumab on patients with laryngeal papillomatosis. The main objective was to assess functional outcomes and efficacy.

Data Sources: Pubmed, Google Scholar, and Web of Science.

Review Methods: Search words were "intralesional bevacizumab" AND "recurrent respiratory papillomatosis." Sources were systematically identified using inclusion and exclusion criteria (ie, study publication must post-date 2000, must be peer-reviewed, investigate patients with RRP, apply bevacizumab intralesionally, not systemically). Findings were then collected and analyzed.

Results: Ten studies were included for analysis. The majority of these studies found an increase in the surgical interval, voice outcomes, and a decrease in tumor burden in most patients. No studies reported side effects or lasting complications related to the bevacizumab injection.

Conclusion: This systematic review provides further evidence for the safety of intralesional bevacizumab injections and their likely positive effect on disease control. Future research would benefit from the implementation of standardized documentation of RRP outcomes.

Keywords

bevacizumab, Avastin, HPV, papillomas, recurrent respiratory papillomatosis

[1] Division of Laryngology, Department of Otorhinolaryngology—Head and Neck Surgery, Mayo Clinic Arizona, Phoenix, AZ, USA
[2] Department of Quantitative Health Sciences, Mayo Clinic Arizona, Scottsdale, AZ, USA

Corresponding author(s):
David G. Lott, MD, Division of Laryngology, Department of Otolaryngology—Head and Neck Surgery, Mayo Clinic Arizona, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA. Email: lott.david@mayo.edu

Introduction

Recurrent respiratory papillomatosis (RRP) is a rare disease of the airway, most commonly affecting the larynx, that results in papillomatous growths. When it predominately affects the larynx it is also referred to as laryngeal

papillomatosis.[1] RRP affects both pediatric and adult populations and can alter vocal production and airway patency with clinical presentations varying between minor voice disturbance to severe airway obstruction.[2] The average onset of RRP varies and has a bimodal age distribution, often presenting either in early childhood or young adulthood.[3] Juvenile transmission of RRP occurs from the mother to child either in utero or during birth.[4] RRP is caused by local infection with Human Papilloma Virus (HPV), which, in adult populations, is passed predominantly through sexual contact.[5] Estimates of juvenile-onset RRP incidence within the United States is estimated to be between 1.45 and 2.93 individuals per 100 000,[6] whereas the incidence of adult-onset RRP has been reported as 1.8 per 100 000 adults.[7]

Two low-risk HPV strains, HPV-6 and HPV-11, account for the majority of cases of RRP and are generally not associated with the development of cancer.[8,9] There is currently no known cure for RRP[10] and surgical excision is the primary method of treatment. Surgical debulking procedures may be performed using various techniques including use of cold excision, laser ablation, and power-driven microdebriders.[11-13] The recurrent nature of the disease causes a significant burden for patients, as they usually require repeated surgical interventions. Adjuvant therapies have become increasingly popular in an attempt to increase the time between surgeries and decrease tumor burden.[11,14-23]

Evidence suggests that overexpression of vascular endothelial growth factor (VEGF) plays a significant role in pathological angiogenesis in tumor cells.[24,25] Bevacizumab (Avastin) is a humanized monoclonal antibody that is known to bind and inhibit VEGF, slowing the growth of blood vessels and inhibiting angiogenesis.[26] Bevacizumab has been approved by the FDA as an injectable medication for the treatment of colon cancer[26] and is used to treat a wide array of other metastatic cancers.[27] Bevacizumab and similar agents can be administered either via an intralesional injection or systemically. Previous studies have shown that systemic use may have more frequent and severe side effects.[28,29]

A previous systematic review in 2017 evaluated outcomes in adult RRP treated with intralesional bevacizumab and cidofovir (a related adjuvant therapy).[30] However, this paper only investigated 2 studies using bevacizumab. Another review published in 2022 investigated intralesional and systemic application of bevacizumab.[29] Again, only 3 studies focusing on intralesional application were included and voice outcomes were not included. The growing number of studies focusing on bevacizumab since this review's publication demonstrates the increasing popularity of this medication as a treatment option. As such, we believed a systematic review looking specifically at bevacizumab was warranted.

Methods

Literature Search

In formulating the research question, a PICO framework was utilized. The patient problem or population was identified as individuals with recurrent respiratory papillomatosis. The intervention was the adjuvant use of bevacizumab. The comparison is among studies reporting findings on the usage of adjuvant bevacizumab with outcomes ranging from clinical resolution to no effect.

A systematic literature search was conducted on April 13, 2023, using Google Scholar, PubMed, and Web of Science to identify English-language or translated studies evaluating the use of intralesional bevacizumab in the treatment of juvenile or adult RRP. Potential studies were then compiled for analysis of their consistency with the inclusion and exclusion criteria. In identifying articles, a search was done using MeSH terms for 2 concepts. The algorithm used was "intralesional bevacizumab AND recurrent respiratory papillomatosis."

To be included in this review, studies had to be peer-reviewed, English-written, and needed to be published within the past 2 decades. They also had to utilize intralesional application of bevacizumab for patients with RRP and were excluded if they used systemic or parenteral application. Finally, they had to report some variety of disease severity outcomes or side effect analysis. Although not all of the selected studies contained all 3 measures of interest (analysis of tumor burden, analysis of time between surgical interventions, and voice outcomes), the selected studies were found to be a representative sample of the research available at the time of investigation and thus worthy of inclusion.

A preliminary search was completed, see *PRISMA Flow Diagram* below. All studies included in this review were analyzed individually and relevant information was cataloged in Table 1. They were organized by the population studied, then by year, and summarized in Table 2.

Table 1. Studies Analysis Summary.

Study number	Author	Publication year	Study type	Sample size	Population
1	Maturo	2010	Retrospective chart review	3	Pediatric
2	Rogers	2013	Prospective cohort study	10	Pediatric
3	Sidell	2014	Retrospective chart review	9	Pediatric
4	Ablanedo-Terraza	2021	Randomized, double-blind, placebo-controlled clinical trial	16	5 Pediatric 11 Adult
5	Zeitels	2009	Retrospective chart review	10	Adult
6	Zeitels	2011	Randomized, double-blind, placebo-controlled pilot study	20	Adult
7	Best	2012	Prospective cohort study	43	Adult
8	Galletti	2021	Case Report	1	Adult
9	Goyal	2021	Case Report	1	Adult
10	Hall	2022	Retrospective chart review	19	Adult

Note. Studies are arranged based on the population studied, then the year of publication, and the alphabetical order of the last name of the first author. They will be referred to based on this study number throughout the paper.

Table 2. Key findings of Investigated Studies.

Study number	Improved surgical interval	Voice score	Tumor burden
1	++	+	+
2	+	++	+
3	++	++	++
4	− −	++	− −
5	+	++	++
6	N/A	+	+
8[a]	++	++	++
9[a]	N/A	N/A	++
10	N/A	N/A	++

Note. + indicates a majority improvement in this measure, ++ indicates all patients improved, − indicates a minority improvement, − − indicates no patients improved. The final study listed was the only study that quantitatively measured tumor burden. Tumor burden for the other studies was inferred based on other referenced outcomes. Study 7 does not report any of these measures and not included in this table.
[a]Studies 8 and 9 were case reports evaluating only 1 individual.

Data Extraction and Analysis

Data was extracted from the identified studies, including study design, population studied, sample size, the time between surgical procedures, disease burden progress, and voice outcomes. Comparisons were drawn between the identified studies with consideration of the differences they exhibited in methodological approaches and follow-up. However, due to the variability and heterogeneity of the included studies regarding their outcome measures, dosage, and timeline, a meta-analysis was not performed.

Results

Of the 131 articles found in Google Scholar, 11 in Pubmed, and 29 in Web of Science, 113 were assessed for eligibility, and 10 were selected for inclusion.[11,15-23] Many of the studies excluded from our review focused primarily on systemic application. The 10 included articles are shown in Table 1.

Study Demographics

The studies evaluated ranged in sample size from 1 to 43 individuals.[11,15-23] The majority of the studies were either pilot studies[11,15,21] or studies focusing on retrospective treatment analysis.[17-20] Six studies evaluated adult patients,[11,16,17,21-23] 3 evaluated pediatric populations,[18-20] and 1 focused on both pediatric and adult patients[15] (Table 1).

Study Treatment Details

All included studies used a 532-nm KTP laser for ablation[11,16-23] apart from 1 case of cold instrument excision.[15] The majority of studies performed their surgical intervention followed by bevacizumab injection.[11,19-23] Study 7 did not couple injection with photoablation for each patient; 63 of the 100 bevacizumab injections were accompanied by KTP laser photoablation.[16] Each study had a unique treatment interval, with some employing a standardized injection interval,[11,19-23] others varying injection intervals based on disease severity,[15,17,18] and others not sharing their injection timeline.[16] Only a few studies indicated the number of sites injected.[11,16,20,21,23] In retrospective studies, treatment timeframes were not standardized (studies 1, 7, and 8).[15,17,18] Treatment windows varied from 2 to 7 weeks, with 24 being the longest number of weeks between treatments reported (study 10).[17] The mean bevacizumab dosage and concentration reported also varied widely between studies. In pediatric groups, the average dosage ranged from 1.25 mg (study 1) to 14.25 mg (study 3, designated as focusing on high dosages), and concentration was not reported.[18,20] Study 5 indicated that patients underwent an initial series of 5 injections, with dosages ranging from 5 to 10 mg in 0.2 to 0.4 mL.[11] Study 4 did not indicate the exact dosage administered, but did indicate that it did not exceed the maximum FDA permitted dose of 50 mg/kg.[15] It also did not indicate whether or not concentration differed between the pediatric and adult populations.[15] Dosage was not reported in Study 9.[23] Studies focusing on adult populations had a larger variance in dosage. Study 6 indicated participants underwent 4 serial sublesional bevacizumab injections ranging from 7.5 to 12.5 mg in 0.3 to 0.5 mL.[21] Other studies employed a higher dose and did not indicate the concentration used, namely study 7 at a range of 15 to 88 mg and study 10, ranging from 25 to 100 mg.[16,17] Three studies did not vary their dosage from patient to patient (studies 2, 5, and 7).[15,18,21]

Setting

Most studies identified whether injections were done in an office or an operating room. Studies 1, 2, 3, and 9 note that the injections were performed in the operating room.[18,21,22,23] Study 5, 6, and 10 state injections were performed in the office.[17] Study 4 does not identify where injections were performed.[11,15,21] Study 7 reported that across participants, 87 injection sessions were done in-office, and the remaining 13 were in the operating room.[16] Study 8 identified that 1 set of injections was performed in the operating room, but does not state in what setting the patient received follow-up injections.[22]

Voice Outcomes

These studies used a variety of different voice outcomes to measure progress, including the Voice Handicap Index (VHI-10),[15] Pediatric Voice Handicap Index,[20] Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V),[20] Voice-Related Quality of Life (V-RQOL),[11,21] Pediatric Voice-Related Quality of Life (PVRQOL),[18,19] and acoustic and aerodynamic measurements.[11,21] Studies 9 and 10 did not provide voice

outcomes.[17,23] In all studies that provided voice outcomes, most patients exhibited improvement in voice outcomes following bevacizumab treatment. Study 4 exhibited decreased vocal handicap index in all treatment groups relative to self, although it did not exhibit improvement relative to placebo. It was also the 1 study that used cold excision instead of KTP laser photoablation.[15] Study 5 indicated that all patients with pre and post-treatment voice measures had improvement in vocal quality. Two of the 3 patients in study 1 saw improved vocal capacity after treatment.[11] Study 6 indicated that all vocal measures displayed statistically significant post-treatment improvement (V-RQOL rating, vocal efficiency, decrease in acoustic noise levels and vocal pitch).[21] In study 2, the median total PVRQOL, emotional PVRQOL, and physical PBRQOL increased by 25.5, 11.3, and 14.3, respectively.[19] Of the 2 patients in study 3 that provided perceptual voice analysis data before and after injection, both exhibited improvements in all components of the CAPE-V scores.[20] Studies 2, 4, and 6 did formal statistical tests and all studies showed that voice outcomes significantly improved.[15,19,21] The majority of studies did not perform formal testing for voice outcomes, so statistical significance cannot be determined.[11,16,18,20,22]

Disease Severity Outcomes

Regardless of discrepancies in administration timelines and measures of progress, the majority of the patients in studies 1, 2, 3, 5, and 8 indicated that patients experienced improved surgical interval, voice scores, and tumor burden (Table 2).[11,16-21] Study 4 did not observe any significant changes with intralesional bevacizumab in any of these measures.[15] While some studies reported the outcomes of their patients,[11,20,21] others presented their results in terms of median change.[15-19,21]

Surgical Interval and Tumor Burden

In study 1, 1 of the 3 patients was symptom-free 6 months post-injection and did not require further operative interventions.[18] The median time between surgical procedures in study 2 increased by 5.9 weeks after bevacizumab injection.[16] The median number of weeks between debulking procedures changed from 6 weeks pretreatment to 12 weeks post-treatment. Concerning tumor burden, Derkay staging decreased by 6 on average.[16] In study 3, all patients had an increased average time interval between injections, with a median improvement of 2.05 times the original interval. A significant improvement was found with a median 58% improvement in post-injection Derkay scores.[20] All of the patients in study 5 had a greater than 90% reduction in recurrence. Only 2 of the 10 patients still required laser treatment and bevacizumab injection. Four out of 10 patients only received injections at an 8- to 12-week interval.[11] Study 6 indicated that 19 of the 20 patients had better disease control in their bevacizumab/KTP-treated vocal fold than in the KTP-laser-only treated vocal fold.[18] A statistically significant increase in time needed between laser treatments was not observed in study 6.[21] The Study 9 bevacizumab regimen was postponed due to COVID-19 and they chose not to provide time between surgical intervals during this period.[23] Study 10 did not provide times between surgical intervals, but they indicated that 11 fewer vocal fold segments were affected by papilloma when bevacizumab was used.[17]

Multiple studies identified that some of their patients achieved remission or clinical resolution by the end of the study.[11,18,20,22] Study 5 identified that 4 out of their 10 patients reached complete clinical resolution and maintained this at 8 to 10 weeks after the cessation of injections, meanwhile, 3 patients developed mild recurrence at that point.[11] In Study 3, 2 out of 9 patients achieved complete remission and had not required additional treatment since the completion of the protocol at the time of publication.[20] It was not indicated at what point in the protocol they achieved remission.[20] The patient in study 8 had complete eradication of

papilloma at their most recent visit, 28 days post-surgery.[22] Many of the patients that were identified to have no significant improvement from bevacizumab injection had originally presented with more severe disease burden.[11,17,20,21] No studies identified negative side effects or consequences of bevacizumab use.[11,15-23]

Discussion

Occurring in both children and adults, RRP can be difficult to manage and is the most frequent cause of childhood hoarseness.[7] The course of this disease can be quite variable from patient to patient.[2] While some patients exhibit a more mild presentation, others experience aggressive growth that requires routine surgical management.[2] Adjuvant therapy is widely understood to be necessary if a patient needs more than 4 surgical procedures per year, experiences multisite spread of the disease, or rapid regrowth that leads to airway compromise.[31] However, given the apparent efficacy and safety, it is safe to offer it to all patients as a prophylactic measure.

The body of knowledge on intralesional bevacizumab has grown over the past decade or so, making the need for an evidence-based review of these findings all the more important. To our knowledge, 2 studies in the past have conducted reviews on intralesional bevacizumab's efficacy as a treatment option for RRP.[29,30] Our study builds upon these, evaluating 10 studies of intralesional bevacizumab injection in RRP patients. Moreover, our analysis includes voice outcomes, which is unique relative to the 2022 study. In order to provide a complete overview of the efficacy of intralesional bevacizumab for RRP in our study, our study included all case reports, case series, and retrospective studies available in medical literature concerning intralesionally administered bevacizumab for RRP.

Overall, the studies exhibited a wide degree of variation in terms of their study types as well as their outcome measures, dosage, timelines, and demographics. Thus, interstudy comparison was limited and no statistical analysis was performed. Specifically, an assessment of heterogeneity and publication bias could not be conducted. Future research would be improved by the implementation of standardized documentation of RRP disease outcomes. One consistency among the studies was that none identified adverse effects from bevacizumab use.[11,15-23]

Studies appeared to use 2 main strategies for a treatment regimen: they either did or did not standardize the bevacizumab treatment regimen among their patients. Moreover, each study had a unique treatment interval, with some employing a standardized injection interval,[11,19,20,21] others varying injection intervals based on disease severity,[15,17,18] and others not sharing their injection timeline.[16] Only a few studies indicated the number of sites injected.[11,16,20,21] No studies indicated that they administered bevacizumab prophylactically.

Of note, study 4 is the only study that did not find improvement with the use of adjuvant intralesional bevacizumab.[15] Perhaps this finding is because bevacizumab inhibits VEGF and thus the growth of new blood vessels. KTP laser photoablation destroys blood vessels in and around the papilloma. It is possible that the combination of KTP laser photoablation and bevacizumab has increased benefits due to blood vessel destruction and limiting vessel regrowth compared to cold excision repair. Further research must be done to compare the effectiveness of these surgical procedures in conjunction with intralesional bevacizumab application. While the common administration of laser therapy may be considered a confounding variable, it is important to note that this study focuses on the adjunctive use of intralesional bevacizumab, not its use in isolation.

While each study had a unique dosage protocol and treatment timeline, the majority of studies indicated an improvement in voice outcomes and disease severity outcomes following bevacizumab use.[11,16-21] In studies that reported voice outcomes, almost all indicated improvement in a majority of patients.[11,15-23] The most

common voice measure among the studies was V-RQOL. Since RRP is a chronic disease in which remission is not typically achieved, nor is there a known cure, improvement in voice-related quality of life is imperative for patient comfort and well-being. Moreover, no studies indicated side effects from bevacizumab application.

Conclusions on the initial disease burden's influence on patient outcomes are conflicting. In study 10, patients with higher initial tumor burden exhibited a larger difference when bevacizumab was incorporated into their treatment plans.[17] Other studies found that patients with lower initial tumor burden (pretreatment Derkay scores) experienced a larger difference when bevacizumab was used (study 6).[21] In study 6, the patient with a pretreatment Deraky score of 13 was symptom-free and did not require further operative interventions 6 months after bevacizumab injection.[21] Meanwhile, a patient with a pretreatment Derkay score of 21 saw an increase to a score of 23 post-treatment. Study 3, the only other study that includes individual patient outcomes, did not see a particular correlation between the intensity of the initial disease burden and the degree of treatment success.[19]

The weaknesses of this review must also be addressed. First, there are only 2 randomized control trials included. Moreover, there is no standardization in reporting between studies, which inhibited the completion of a meta-analysis and thus the identification of any statistical significance. In terms of treatment options present, most studies used KTP which is not representative of the different methods currently used for surgery. There was also a significant variance in the dosage and concentration of bevacizumab. All of the presented studies may be prone to publication bias, which may sway the perceived efficacy of intralesional bevacizumab as an adjuvant. Moreover, given that some studies provided data about individual patients while others provided averages, it is difficult to distinguish what makes intralesional bevacizumab a more effective treatment for some patients over others.

The majority of the studies included in this systematic review reported an improvement in the surgical interval, voice outcomes, and tumor burden following adjuvant bevacizumab use.[11,16-21] As such, there is support for the use of either adjuvant or prophylactic intralesional bevacizumab injections in the management of RRP. Studies exhibited a wide degree of variation in terms of their outcome measures, dosage, timelines, and demographics, which limits the accuracy of interstudy comparison. Future studies on the use of intralesional bevacizumab for RRP would benefit from standardized documentation of outcome measures so that more effective comparisons can be made.

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Author Contributions

Ursula E. Gately, BS: Project Concept, Project Design, Statistical Analysis, Results Analysis, and Manuscript Preparation. Nan Zhang, MS: Project Design, Statistical Analysis, Results Analysis, and Manuscript Preparation. William E. Karle, MD: Results Analysis and Manuscript Preparation. David G. Lott, MD: Project Concept, Project Design, Statistical Analysis, Results Analysis, and Manuscript Preparation.

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ORCID iDs

Ursula E. Gately https://orcid.org/0000-0002-7755-2730

David G. Lott https://orcid.org/0000-0001-6541-9687

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