

Safety of Intranasal Bevacizumab (Avastin) Treatment in Patients with Hereditary Hemorrhagic Telangiectasia-Associated Epistaxis

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Objectives/Hypothesis: Assess for complications of intranasal Bevacizumab application in patients with hereditary hemorrhagic telangiectasia (HHT)-associated epistaxis.

Study Design: Retrospective chart review.

Methods: In 58 patients presenting with recurrent HHT epistaxis, Bevacizumab was applied intranasally either as a submucosal injection or as a topical spray between October 2006 and June 2010. In many of the injected patients, the potassium titanyl phosphate (KTP) laser was used adjunctively for vessel photocoagulation. A phone interview was performed in July 2010 to assess for treatment complications.

Results: Of the 58 treated patients 52 were contacted. Patient surveys were performed 1.5 to 46 months following their initial Bevacizumab treatment. Within the treatment population, five patients had sustained a septal perforation. Notably, these patients were treated early in the study period at which time the cartilaginous septum was often both injected and lasered. Subsequently, the treatment protocol was changed and the cartilaginous septum was neither lasered nor injected. After these changes were made no additional septal perforations were identified. No other adverse events were associated with intranasal Bevacizumab treatment.

Conclusions: Bevacizumab applied as either a submucosal injection or as a topical nasal spray, with or without application of the KTP laser, is a safe treatment regimen. Still, when Bevacizumab injections are performed, the cartilaginous nasal septum should be avoided as patients may develop septal perforations.

Key Words: Epistaxis, hereditary hemorrhagic telangiectasia, Osler Weber Rendu, Bevacizumab, Avastin.

Level of Evidence: 2b

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), aka Osler-Weber-Rendu Syndrome, is an inherited autosomal dominant vascular dysplasia affecting 1:10,000 Caucasians.¹ Further, according to Senate bill 508, 2009, 70,000 people in the United States suffer from HHT.² Over time, patients develop mucocutaneous telangiectasias as well as visceral arteriovenous malformations. Most commonly, the telangiectasias lining the nasal mucosa bleed with 95% of patients developing a lifelong recurrent epistaxis that worsens with age.³ As their nosebleeds become more severe, patients require intravenous iron supplementation as well as blood transfusions to stay alive. Until recently, management of HHT has largely been surgical with treatments including electrocautery, laser photocoagulation, septal dermoplasty, as well as nasal closure with the Young's procedure.

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As an autosomal dominant disease, several genes have been associated with HHT including Endoglin, Alk-1, and SMAD-4.⁴ Interestingly, many of these genes are members of the transforming growth factor-beta (TGF- β)—vascular endothelial growth factor (VEGF) signaling cascade. Moreover, prior studies demonstrate HHT patients have elevated plasma and mucosal levels of VEGF and TGF- β .⁵ With this pathology in mind, Bevacizumab, a humanized monoclonal IgG1 VEGF inhibitor, was introduced as a potential therapy for HHT associated epistaxis. With Bevacizumab administration, both intranasally and intravenously, patients have demonstrated significant improvement in epistaxis frequency and severity.^{6–8}

Of note, when using Bevacizumab doses intended to treat metastatic cancer, typically 5 to 15 mg/kg every 2 weeks, serious side effects have been reported.⁹ These include gastrointestinal perforation in 0.3% to 2.4%, delayed wound healing (up to 1 month after treatment), new onset hypertension in 5% to 18%, and extranasal hemorrhagic events in 1.2% to 4.6% of treated patients.⁹ In ophthalmology, however, using 1.25 mg doses to treat retinal neovascularization, the complication rate is quite low at 0.21% or less.¹⁰ Most commonly, identified adverse effects included blood pressure elevation, corneal abrasion, mild discomfort, and inflammation uveitis.¹⁰ To date, the complication profile for low-dose intranasal Bevacizumab treatment remains undefined.

TABLE I.
Treatment Details.

Bevacizumab Administration	Number of Patients	Mean Dose (Standard Deviation)	Total Number of KTP Laser Treatments during Bevacizumab Application
Topical	26	98 mg (45)	0
Submucosal	34	138 mg (106.46)	42 applications (in 30 patients)
Total (submucosal + topical)	52	139 mg (116.0)	42 applications (in 30 patients)

Eight patients received both topical and submucosal intranasal Bevacizumab administrations, none concurrently.

METHODS

Between October 2006 and June 2010 58 HHT epistaxis patients were seen and treated at the UCSD Nasal Dysfunction Clinic. Intranasal Bevacizumab was administered in all patients either topically and/or submucosally. Submucosal Bevacizumab dosing ranged from 25 to 100 mg at each application, whereas topical applications were between 50 and 100 mg. In addition, depending on epistaxis severity, patient preference, and prior response to Bevacizumab some patients were treated on multiple occasions. In 34 of the injected patients photocoagulation with the KTP laser was also performed. To determine possible adverse side effects associated with intranasal Bevacizumab, a literature review including a search of manufacturer data was performed. A questionnaire was subsequently developed that included associated common and serious reactions.

Following approval from the UCSD internal review board an attempt to phone all patients was made. Patients were asked about the development of common adverse reactions that included new onset nasal obstruction, tinnitus, dry mouth, voice changes, headache, runny nose, asthma, allergic rhinitis, or changes in their sense of smell. More serious events such as new onset bleeding outside of the nose, septal perforation, gastrointestinal perforation, poor wound healing, hypertension, proteinuria, thromboembolism, congestive heart failure, fistula formation, seizure, or vision loss were also queried. For all contacted patients, the questionnaire was completed and all adverse events were recorded.

RESULTS

Fifty-two of 58 patients were contacted in July 2010. Patients were contacted between 1.5 and 46 months following their initial Bevacizumab treatment. There was a slight majority of male patients (32 of 68, 55%) with a mean age of (54.99; SD = 11.8, range: 22–81). Treatment details are included in Table I. Twenty-six patients received topical Bevacizumab (mean total dose 98 mg) and 34 patients received submucosal Bevacizumab (mean total dose 138 mg). Also, the KTP laser was only used at the time of submucosal Bevacizumab injection. In addition, patients receiving submucosal injections typically had longer follow-up times compared to patients receiving a topical application, as we only began topical therapy a year ago (see Table II).

Identified complications associated with intranasal Bevacizumab treatment were largely restricted to the development of a posttreatment septal perforation in five patients. Notably, each of these patients were treated with both submucosal Bevacizumab and with the KTP

laser along the bilateral cartilaginous septum. Once this complication was identified, a result of impaired wound healing, the cartilaginous septum was neither injected nor lasered. Thereafter, no further septal perforations were appreciated. In addition, no patients developed any of the aforementioned common or serious events following Bevacizumab treatment. Still, some patients had baseline gastrointestinal bleeding, hypertension, and nasal obstruction that was unchanged before and after nasal Bevacizumab administration.

DISCUSSION

Despite documented improvements in nasal bleeding, the side effect profile of low-dose intranasal Bevacizumab remains undefined. Originally, Bevacizumab was developed as a chemotherapeutic agent that targets increased VEGF expression in cancer metastasis. When treating metastatic disease, intravenous dosing schedules range between 5 and 15 mg/kg depending on the cancer being treated. In addition, these treatments were administered every 2 weeks until patients demonstrated drug toxicity or disease progression. For example, a 70-kg male with metastatic colorectal cancer would receive 350 mg of intravenous Bevacizumab every 2 weeks for treatment periods ranging from months to years. In this study, 25 to 100 mg of Bevacizumab was administered submucosally or topically never more frequently than every 2 months. Moreover, although not measured, it is very likely that the intravenous absorption for both nasal administration modalities is minimal. As such, the complications associated with high-dose intravenous administration (such as gastrointestinal perforation) were not seen with the low doses used for HHT epistaxis. This study, while limited in patient numbers, suggests that intranasal Bevacizumab is safe with a paucity of systemic side effects associated with low-dose intranasal administration.

Still, there are significant local risks when using Bevacizumab in HHT patients. In particular, this study suggests that Bevacizumab when applied to the cartilaginous septum inhibits wound healing and predisposes patients to septal perforation particularly when used in conjunction with a laser.

CONCLUSION

Intranasal Bevacizumab has shown benefit in HHT epistaxis. Although significant systemic complications

TABLE II.
Follow-up Survey Details.

Bevacizumab Treatment	Number of Contacted Patients	Mean Time Between First Avastin Dose to Interview (Standard Deviation)
Topical	21	3.4 months (2.2)
Submucosal	31	19.3 months (14.4)
Total (submucosal + topical)	52	12.9 months (13.7)

have been associated with chemotherapeutic dosing schedules, no significant systemic adverse effects were identified in 52 HHT patients treated with low-dose intranasal Bevacizumab (25–100 mg). Despite a lack of systemic side effects, intranasal submucosal Bevacizumab does inhibit local wound healing. Moreover, patients are at risk of developing a septal perforation if Bevacizumab is injected into the cartilaginous septum.

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