Intranasal Bevacizumab for HHT-Related Epistaxis

Study Protocol and Statistical Analysis Plan

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RESEARCH STRATEGY

A Randomized Controlled Trial of Bevacizumab for HHT-Related Epistaxis

SIGNIFICANCE

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder characterized by systemic vascular malformations that result from mutations of the ENG gene, which encodes for factors in the vascular endothelial growth factor (VEGF) pathway. HHT is diagnosed by the Curacao Criteria including the presence of epistaxis; telangiectasias or vascular malformations in the lungs, liver, or nervous system; and a positive family history involving a first-degree relative[1]. One of the most common presentations of this disease is recurrent and profound epistaxis, with many patients reporting more than 4 epistaxis episodes in a day, many lasting up to an hour. HHT-related epistaxis often results in severe anemia requiring intravenous iron and repeated blood transfusions, and also carries significant psychosocial disability relating to impaired quality of life and work absenteeism. Multiple approaches to treatment have been described, including electrocautery, laser treatment, embolization, septodermoplasty, and as a last resort, Young's procedure, involving closure of the nasal vestibule[2]. These approaches are largely palliative, with variable effectiveness, and almost always require repeated procedures for chronic management of bleeding[3]. There is a great need for the development of new treatment options for reducing the medical morbidity and quality of life impairment associated with refractory epistaxis in HHT.

Recently there has been promising data suggesting that inhibition of angiogenesis may be an effective strategy for managing HHT-related bleeding. Circulating concentrations of VEGF are significantly elevated in HHT, making VEGF an attractive therapeutic target[4]. Preliminary studies suggest that bevacizumab, a recombinant monoclonal antibody that inhibits the biologic activity of VEGF, can significantly improve epistaxis severity when topically applied, locally injected, or intravenously administered[5]. However, these early pilot studies of bevacizumab have been limited exclusively to retrospective case series. As yet, there has been no prospective double-blind placebo controlled trial to establish the role of bevacizumab in the treatment of HHT-related epistaxis.

INNOVATION

The Stanford Sinus Center is a tertiary referral center for advanced rhinologic care, with a catchment area that is focused on northern California (population 13 million), but also includes southern California, Nevada, southern Oregon and Hawaii. The clinical volume of the center encompasses approximately 6000 clinic visits and 600 operations per year. Included in the patient population is a robust base of HHT patients who return to Stanford regularly for surgical management of epistaxis. Dr. Hwang, Director of the Sinus Center, has an active interest in HHT; he has been a guest speaker at the national HHT patient conference and has published on surgical techniques for HHT-related epistaxis. Complemented by our team of dedicated research fellows and resources for clinical research support available through the Stanford School of Medicine, the Sinus Center is poised to carry out the first randomized, double-blind, placebo-controlled clinical trial of bevacizumab injection versus saline control for the management of HHT-related epistaxis, by which we hope to shift the current clinical practice paradigms in treating this debilitating disease.

APPROACH

Preliminary Data

Several retrospective studies in the recent literature have demonstrated that the use of bevacizumab as an adjunct to electrocautery or laser treatment for epistaxis related to HHT is associated with additional benefit in reducing epistaxis symptoms[6]. When compared to a group of patients who received laser treatment alone, the group who received bevacizumab in addition to laser treatment had a reduction in the frequency of epistaxis, number of blood transfusions, disability, and effect on social life[7]. There is good evidence to support that intranasal use of low-dose bevacizumab is also safe. Systemic use of bevacizumab as a treatment for metastatic cancer using doses of up to 5 to 15mg/kg has been associated with serious side effects[8]. However, bevacizumab has been used extensively in ophthalmology in low doses to treat neovascularization with low complication rates on the order of 0.21% or less[9]. In a chart review of 58 patients who received bevacizumab by intranasal submucosal injection or topical spray, five patients sustained septal perforation. The authors note that the treatment protocol was changed such that injection to the cartilaginous septum was avoided, and after this no further septal perforations were identified[10].

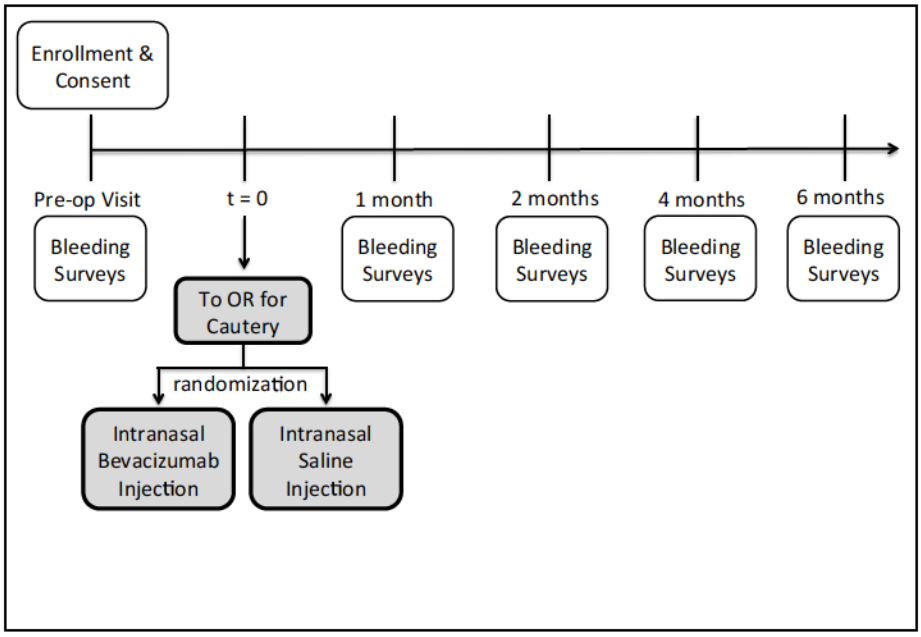
Subsequently, a study from 2012 developed a standardized injection protocol for bevacizumab treatment based on the vascular anatomy of the nose with attention to avoiding injection of the cartilaginous septum[11]. This injection protocol used 100mg of bevacizumab injected submucosally, (50mg per side), into four locations within the nose: the sphenopalatine area, the upper part of the bony septum, the upper part of the lateral nasal wall, and the anterior part of the nasal floor. This study found a significant improvement in the post-treatment epistaxis frequency and severity for the 8 patients enrolled in the study, but without a control group for comparison; no incidents of septal perforation were noted.

Experimental Plan

Specific Aim 1: Determine if intranasal bevacizumab injection decreases epistaxis frequency and severity compared to placebo with HHT

Rationale and Hypothesis

Based on existing level 4 evidence that suggests that bevacizumab injection is beneficial in the management of HHT-related epistaxis, we hypothesize that patients who receive intranasal injection with bevacizumab at the time of electrocautery treatment will have an improvement in the frequency and severity of epistaxis compared to patients who receive injection of saline control.



Approach

Patients to be included in this study are those who have a diagnosis of HHT confirmed by the Curacao Criteria, who are to undergo treatment with electrocautery in the operating room under endoscopic visualization, and who are at least 18 years of age. Patients will be excluded if they have had any new treatments for their epistaxis within the 8 weeks prior to starting the trial, or if the patient is a minor or is pregnant. After informed consent is obtained, patients will be randomized to either bevacizumab injection or saline control. The Stanford Hospital Investigational Pharmacy will perform all randomization, drug storage and management, as well as mixing and packaging for double-blinded injection of bevacizumab or saline control. Patients enrolled in the study will undergo standard-of-care bipolar electrocautery of nasal telangiectasias in the Stanford Ambulatory Surgery Center operating room. At the time of electrocautery, patients will receive intranasal injection of either study drug or saline control. The surgeon performing the injection will be blinded to whether injection is composed of bevacizumab or saline control. Bevacizumab will be mixed by the Stanford Hospital Pharmacy to a total dose of 100mg in 4mL, and 50mg (2mL) will be injected into each side of the nose. Injections will be performed according to the standardized four-point injection protocol (0.5mL/site) based on the vascular anatomy of the nose published in 2012 by Dheyauldeen et al[13]. In accordance with this protocol, care will be taken to avoid injection of the cartilaginous nasal septum to avoid the risk of nasal septal perforation. At the pre-operative appointment and then again following operative electrocautery with injection, patients will be followed with serial surveys regarding their epistaxis symptoms administered at 1 month, 2 months, 4 months, and 6 months post-injection (**Figure 1)**. The time points selected for this analysis were based upon the study by Karnezis et al., which followed Epistaxis Severity Scores on a monthly basis up to one year after submucosal injection of bevacizumab[12].

The majority of studies of HHT-related epistaxis use the Epistaxis Severity Score (ESS) as a standardized and reproducible outcome measure for control of epistaxis[13]. This validated measure was developed by a panel of HHT care providers and a focus group of patients to determine the factors that best correlate with epistaxis severity. It is composed of six factors that are independent predictors of self-described epistaxis severity, each one weighted by coefficients from the model derived (**Figure 2)**. In order to more accurately capture the change in epistaxis symptoms over time at each of the data points proposed in this study, we will modify the ESS questions slightly to focus on the symptoms experienced over the preceding month (for example, instead of asking “have you ever sought medical attention for nose bleeding?” our questionnaire will be modified to ask “have you sought medical attention for nose bleeding within

Data Sheet for the Calculation of the Epistaxis Severity Score for Hereditary Hemorrhagic Telangiectasia.

How often do you TYPICALLY have nose bleeding? (coefficient 0.14)

0 — Less than monthly
1 — Once per month
2 — Once per week
3 — Several per week
4 — Once per day
5 — Several each day

How long do your TYPICAL nose bleeds last? (coefficient 0.25)

0 — <1 minute
1 — 1–5 minutes
2 — 6–15 minutes
3 — 16–30 minutes
4 — >30 minutes

How would you describe your TYPICAL nose bleeding intensity? (coefficient 0.25)

0 — Not typically gushing
1 — Typically gushing or pouring

Have you every sought medical attention for nose bleeding? (coefficient 0.30)

0 — No
1 — Yes

Are you anemic (low blood count) currently? (coefficient 0.20)

0 — No
1 — Yes

Have you ever received a red blood cell transfusion specifically because of nose bleeding? (coefficient 0.31)

0 — No
1 — Yes

Six questions are answered, the number of the response is multiplied by the respective coefficient, and the sum of these gives the raw epistaxis severity score.

Figure 2. Epistaxis Severity Score. Comprised of 6 independent predictors of epistaxis severity. (From Hoag *et al., 2010)*

the last month?").

Statistical Considerations

The primary endpoint of this study is to determine if there is a significant difference in the change in Epistaxis Severity Score in the bevacizumab group compared to the group who received injection of saline control. Based on previously published data, a reasonable therapeutic target is a difference in the change in ESS score between groups of 2 points on the ESS scale. In order to have 80% power at this target, we will require 17 informative patients per arm of this trial. To account for loss to follow-up and other unforeseen attrition, we propose to study 20 patients in the bevacizumab group and 20 patients in the saline control group for a total accrual goal of 40 patients. This estimate is in fact based on a conservative power calculation as it is based on anticipating a standard deviation within the ESS scoring system of 2, however other published data within the literature suggests that a more likely standard deviation of 1 can be achieved with the ESS grading scale. A two-sample t-test power calculation was used to perform this power analysis.

Expected Results

Our primary goal is to determine if intranasal bevacizumab injection as an adjunct to operative electrocautery provides any additional benefit in the management of epistaxis frequency or severity or need for repeated interventions in patients with HHT, as measured by the ESS scoring system. We expect that patients treated with bevacizumab will have a significantly greater reduction in their ESS grading than patients injected with the saline control when comparing pre-and post-injection ESS grades. We anticipate that differences in epistaxis symptoms between the two groups may be difficult to discriminate at the 1 month time point, as both groups will likely show an improvement in their epistaxis related to the operative electrocautery at this early time point, however based on the time points in the Karnezis trial the 1 month time point will allow us to establish a new post-operative baseline for epistaxis symptoms. We would anticipate significant differences to manifest at the 2 month, 4 month, and 6 month time points. Data will be analyzed using an ANCOVA model, testing for the change in the two arms while allowing appropriate adjustment for the baseline value.

Potential Problems and Alternative Approaches

A the study proceeds, we anticipate the possible need to administer ESS surveys at additional time points to optimize our understanding of the contribution of bevacizumab injection with electrocautery on epistaxis symptoms over time. The selected time points were based upon data available from the aforementioned Karnezis study which administered ESS surveys monthly after bevacizumab[9]. However, because this retrospective analysis did not include a control arm it is difficult to predict at what time point we will see the maximum spread in the change of ESS will be seen when comparing the drug intervention versus saline control group.

Specific Aim 2: Determine if intranasal bevacizumab injection results in a greater improvement in quality of life compared to placebo when used in conjunction with electrocautery for patients with HHT

Rationale and Hypothesis

Given the known negative impact of recurrent refractory epistaxis on quality of life in patients with HHT, we hypothesize that patients who undergo blinded intranasal injection with bevacizumab will demonstrate improved post-operative quality of life and health status scores than patients who receive injection with saline control.

Approach

We will assess global health outcomes and quality of life using the Short Form-36 (SF-36) Health Status Questionnaire. This short survey is a validated health status survey that was developed out of two large epidemiological studies, the Health Insurance experiment, and the Medical Outcomes Study, and has been reliably used in a number of chronic disease states[14]. This survey was further validated in its ability to measure the health of patients with epistaxis due to HHT by Lennox et al. in 2005, who demonstrated the utility of SF-36 as an outcome measure in assessing efficacy of treatment of HHT-related epistaxis[15].

Patients enrolled in this study will complete the SF-36 surveys in conjunction with the ESS surveys at baseline (pre-operative), 1 month post- treatment, 2 months post-treatment, 4 months post-treatment, and 6 months post-treatment. The SF-36 queries various quality of life parameters experienced by the patient over the preceding four-week period, which will align well with the 4-week symptom window of our modified ESS survey results for purposes of outcomes analysis.

Expected Results

We expect that health status scores will improve in all patients after operative electrocautery treatment of telangiectasias. However we expect to see a greater magnitude of improvement and possibly a prolonged quality of life benefit in the group of patients randomized to receive bevacizumab injection versus those who receive injection of saline control. Data will be analyzed using an ANCOVA model, testing for the change in the two arms but adjusting for the baseline value.

Potential Problems and Alternative Approaches

Patients in the study may experience concurrent HHT-related complications in other organ systems such as pulmonary AV malformations, hepatic involvement, or gastrointestinal bleeding, which can adversely affect global quality of life and health status. In such circumstances, the SF-36 may be less sensitive for detecting changes in quality of life and health status specific to the treatment for epistaxis. A newly introduced adjunctive survey which focuses on epistaxis-specific quality of life items may be administered as a complement to the SF-36 if the results of the SF-36 alone are not sensitive enough to detect a change[16].

Specific Aim 3: Determine the cost-effectiveness of intranasal bevacizumab injection compared to placebo when used in conjunction with electrocautery

Rationale and Hypothesis

In a time of increasing health care expenditure, there is growing concern pertaining to the fiscal sustainability of the US health care system. In 2009, the USA spent an estimated $7,960 per capita on heath care with approximately 17.4% of its GDP and spending is increasing on average of 4% per year[17]. This data emphasizes the importance of critically evaluating the delivery of both current and future interventions in order to ensure resource allocation is cost-effective.

One hundred milligrams of bevacizumab costs approximately $600 as a wholesale acquisition[18], but the indirect cost of recurrent epistaxis in terms of patient productivity can lead to significant economic losses to society. Frequent epistaxis related to HHT is itself disabling, worsened by the additional costs of repeated operating room fees, anesthesia costs, recurrent blood transfusions and intravenous iron treatments, and repeated emergency room visits. We hypothesize that patients who undergo blinded intranasal injection with bevacizumab with have lower post-operative epistaxis-related costs (both direct and indirect) than patients who receive injection of saline control. We also hypothesize that the incremental cost effectiveness ratio (ICER) of bevacizumab injection will be

considered cost effective compared to saline injection based on a willingness to pay threshold of $50,000 per quality adjusted life year (QALY).

Approach

The economic evaluations will take the societal perspective. Direct cost collection and estimation will follow the three steps outlined by Smith and Rudmik[19]. Indirect costs will be estimated using the human capital approach for defining productivity costs. Productivity costs will include both presenteeism and absenteeism. Absenteeism will be quantified using the Quantity and Quality Questionnaire[20]. Based on current recall recommendations, absenteeism will be quantified by asking both the number of full work days missed and the number of work hours missed due to HHT-related epistaxis in the last 3 months[16-18]. All cost related questionnaires will be completed at baseline and 6 months post-injection. Lost productive time will be assessed by measurement of per-person work days lost due to epistaxis, as well as measurement of lost productivity time due to disease-related reduced work performance. Household productivity loss will be evaluated by asking patients how much time is used at home to care for epistaxis each day. This lost productive time can then be monetized based upon median annual income data and used to approximate the productivity cost to society.

The primary outcome for our CEA will be the cost per QALY. The QALY is based off the patients' preference for being in a particular health state. This preference is equal to a health state utility score and is ranked from 0.0= "death" to 1.0= "perfect health". For this economic evaluation, the utility scores will be obtained using the SF-6D instrument. The SF-6D is based on the general QoL instrument called the Short-Form 36 (SF-36) and Short form 12 (SF-12)[21]. Health state utility scores (SF-6D) are derived from responses to 6 separate items indicated on both the SF-36 and SF-12 using a commercially available weighted algorithm derived by the Department of Health Economics and Decision Science at the University of Sheffield, Sheffield, United Kingdom[22]. This algorithm application is compatible with most commercially available statistical software packages and was used to calculate standardized health state utility values from follow-up survey responses provided by each study subject. The utility scoring system is based on standard gamble valuation technique performed in the United Kingdom general population.

Expected Results

We expect that patients who are randomized to receive bevacizumab injection at the time of operative electrocautery will have a significant reduction in both direct and indirect costs including paid work days missed, reduction in work performance, and household days lost to time spent caring for their epistaxis when compared to patients who are randomized to the saline-control injection group. We hypothesize that injection of bevacizumab at the time of electrocautery will translate to a cost-effective intervention compared to injection of saline for patients with HHT.

Potential Problems and Alternative Approaches

Our patient population seeking treatment at a tertiary medical center is likely to represent a selected cohort of individuals who may have more severe HHT manifestations. As such, the productivity costs for these patients may be skewed higher. Other limitations of performing an economic evaluation along side a RCT include challenges with calculating adequate power for the primary economic outcome. Based on recommendation by Drummond et al[23], we powered this study for the most important economic endpoint which is epistaxis symptom severity, since this outcome will likely drive the majority of health care resource consumption. To prevent the inclusion of trial driven costs into the CEA, we will exclude any costs incurred as a result of being in the trial.

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