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Bevacizumab in Hereditary Hemorrhagic Telangiectasia-Associated Epistaxis: Effectiveness of an Injection Protocol Based on the Vascular Anatomy of the Nose

Sinan Dheyauldeen, MD; Amy Østertun Geirdal, SW, MHs; Terje Osnes, MD, PhD;
Liv Sofie Vartdal, MD; Ralph Dollner, MD, PhD

Objective/Hypothesis: To evaluate the effectiveness of a standardized intranasal bevacizumab injection in treating hereditary hemorrhagic telangiectasia (HHT)-associated epistaxis.

Study Design: Prospective pilot study.

Methods: A total dose of 100 mg bevacizumab (25 mg/mL Avastin) was injected submucosally, 50 mg on each side. A total of 0.5 mL was injected in the sphenopalatine area, upper part of bony septum, upper part of the later nasal wall, and the anterior part of nasal floor. No cauterizations or laser therapy were done during or after the procedure. The hemoglobin level and grades of epistaxis were recorded before and monthly after the procedure. The IFT grading system (intensity [I], frequency [F] of epistaxis, and the amount of blood transfusion [T]) and epistaxis severity score (ESS) for hereditary hemorrhagic telangiectasia system were used. Quality of life (QoL) was evaluated before and 4 weeks after the procedure using the Short Form-36 Health Survey questionnaire, Cantril's Self-Anchoring Ladder questionnaire, and Slotosch disease-specific QoL questionnaire.

Results: A significant improvement was found in IFT grading ($P = .007$), ESS grading ($P = .001$), and hemoglobin level ($P = .01$). The QoL differences were statistically not significant.

Conclusions: The four-injection site technique of intranasal administration of bevacizumab is an effective treatment option in HHT-associated epistaxis, at least on the short-term effect. Long-term and comparative studies are needed to further evaluate the significance of this treatment modality.

Key Words: Epistaxis, Osler disease, hereditary hemorrhagic telangiectasia, bevacizumab, local treatment, intranasal, treatment technique, vascular anatomy of the nose, quality of life.

Level of Evidence: 4.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a rare, vascular, autosomal dominant disease, characterized by bleeding usually in the form of epistaxis and less obvious in the form of gastrointestinal bleeding. Arteriovenous malformations (AVM) of the lung, liver, and central nervous system are also known clinical features. Epistaxis is the most common and most disturbing symptom in HHT.[1–4] A wide variety of treatment options have been developed for the control of HHT-associated epistaxis.[1,5] Nostril closure by modified Young's procedure is so far the only long-lasting effective treatment to control HHT-associated epistaxis.[6,7]

Abnormal vessels in HHT develop because of altered transforming growth factor-β signaling during vascular development and hemostasis,[8–10] leading to angiodysplasia.[11] Angiogenic factors, such as the vascular endothelial growth factor (VEGF), are found at high levels in plasma of HHT patients,[10,12–13] and seem to play a crucial role in the pathogenesis of HHT. This identifies VEGF as a possible therapeutic target in HHT.

Bevacizumab is a recombinant, humanized, monoclonal antibody that binds to and inhibits the biological activity of VEGF, and therefore prevents endothelial cell proliferation and angiogenesis.[7,14] It has been used in the treatment of HHT-associated complication since 2006.[2,15,16] The intranasal administration of bevacizumab has also been described with different doses and different techniques.[14,17–20]

The aim of the study was to evaluate the efficacy of a standardized and anatomically based method of intranasal administration of bevacizumab in a prospective

From the Department of Otorhinolaryngology (S.D., T.O., L.S.V., R.D.), Head and Neck Surgery, Division of Surgery and Neuroscience, and Department of Medical Genetics (A.Ø.G.), Oslo University Hospital–Rikshospitalet, Oslo; Faculty of Social Science (A.Ø.G.), Oslo and Akershus University College of Applied Sciences, Oslo, Norway; and the Department of Otorhinolaryngology (R.D.), Head and Neck Surgery, University Hospital Mannheim, Mannheim Medical School, University of Heidelberg, Heidelberg, Germany.

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Send correspondence to Sinan Dheyauldeen, MD, Department of Otorhinolaryngology, Head and Neck Surgery, Division of Surgery and Neuroscience, Oslo University Hospital–Rikshospitalet, Postbox: 4950 Nydalen, 0424 Oslo, Norway. E-mail: saldeen@ous-hf.no

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TABLE I.
Age and Gender Distribution of the Patients With Pre- and Post-Treatment Epistaxis Grades and Hemoglobin Levels.

Patient No.	Gender	Age, yr	IFT Epistaxis Grading		ESS Epistaxis Grading		Hemoglobin, g/dL		Observation Period, wk
			Before	After	Before	After	Before	After	
1	F	68	25	3	6.44	2.61	10.1	12.0	12
2	M	43	12	2	5.52	1.96	11.1	14.0	10
3	F	53	25	2	8.25	2.49	13.2	15.4	8
4	F	36	15	4	4.70	3.02	11.7	13.4	8
5	F	71	11	4	6.98	2.49	10.4	11.1	8
6	M	53	9	3	4.98	2.49	11.0	17.1	10
7	F	69	7	7	4.98	4.98	8.4	8.0	10
8	M	59	10	3	6.20	2.49	8.5	13.0	10
Mean		56.5	14.3	3.5*	6.00	2.82†	10.6	13.0‡	9.5

*$P = .007$.
†$P = .001$.
‡$P = .01$.
IFT = intensity (I), frequency (F) of epistaxis, and the amount of blood transfusion (T); ESS = epistaxis severity score.

manner. The efficacy of the treatment was measured by two epistaxis grading systems, hemoglobin level, and three types of quality-of-life (QoL) measures.

MATERIALS AND METHODS

Patients

Eight patients with definite HHT diagnosis according to Curaçao diagnostic criteria[21] were included in the study. Five of the eight patients were female. The mean age was 56.5 years (standard deviation [SD], 12.7; range, 36–71 years) (Table I). All patients had been treated previously for their HHT-associated epistaxis with repeated pulsed-dye laser, diode laser, or argon plasma cauterization without considerable clinical improvements. Additional medical therapy, like oral and topical tranexamic acid, oral tamoxifen or raloxifen, and topical estrogen, were tried without significant benefit. One of the patients was previously operated with septodermoplasy. Seven of the patients needed oral or intravenous iron supplements. Two of the included patients had previous septum perforation. Three out of the eight patients complained of HHT-related gastrointestinal bleeding, three had pulmonary AVMs, one patient had HHT-related pulmonary hypertension with cardiac complication, another had hepatic AVM, and one patient complained of intractable migraine without AVM.

The grades of epistaxis were recorded during direct interview with the patients before the procedure and afterward monthly by telephone interview. We used our previously published IFT grading system, which depends on the intensity (I), the frequency (F) of epistaxis, and the amount of blood transfusion (T) during the period of the last 4 weeks.[22,23] Additional grading was done using the epistaxis severity score (ESS) system.[24]

QoL was evaluated before and 4 weeks after the procedure by the health-related QoL questionnaire (HRQoL) Short Form-36 Health Survey (SF-36).[25,26] In addition, overall QoL was evaluated by the Cantril Self-Anchoring Ladder (CL), which is based on one question: "How is your life?" The patients rated their answers on a scale between 0 and 10, with 0 = worst possible QoL and 10 = best possible QoL.[27] The higher the score of the SF-36 and CL the better the QoL. Furthermore, the disease-specific QoL was evaluated by asking the patients, "To which level does HHT impact your QoL?" The answers were rated by the patients on a 10-point scale, where 1 corresponds to no impact on quality of life and 10 corresponds to the worst possible quality of life,[28] with higher score indicating that the disease has more impact on QoL.

Procedure

Anesthesia and preoperative medication. The procedure was done under local anesthesia with light sedation in seven out of the eight patients. The patients received 1 to 2 g paracetamol and 5 mg oxycodone (OxyNorm; Mundipharma Pharmaceuticals Ltd., Dublin, Ireland) orally 30 to 60 minutes preoperatively. Some patients also received 5 to 7.5 mg midazolam. Gentle nasal packing was done with 50-cm-long and 2-cm-wide gauze soaked in a solution of topical tetracaine (16 mg/mL) and adrenalin (0.2 mg/mL) for 30 to 60 minutes. Repeated doses of fentanyl (50 μg/mL) were given intravenously under the procedure.

Monitoring. Physiologic monitoring of the patients during the procedure was carried out by monitoring blood pressure, oxygen saturation by pulse oximeter, and three-lead electrocardiography.

Bevacizumab dosage. A total dose of 100 mg bevacizumab and 25 mg/mL Avastin (Roche, Basel, Switzerland) was injected submucosally at four anatomical sites.

Injection technique. Each of the following areas was injected with 0.5 mL bevacizumab on each side: 1) the sphenopalatine area, 2) upper part of bony septum, 3) upper part of the lateral nasal wall, and 4) the anterior floor of the nose. These four areas correspond to the points of entry of the main arteries responsible for the blood supply to the nasal mucosa, which are the sphenopalatine artery, the anterior ethmoid artery, posterior ethmoid artery, and greater palatine artery (Fig. 1).

A long 23-gauge needle was used. The procedure was endoscopically assisted, using a 0° and/or 30° rigid nasal fiberoptic scope (Storz, Tuttlingen, Germany). Bleeding during the procedure was treated by additional tetracaine/adrenalin pack or packing with Surgicel (Ethicon, Somerville, NJ). No cauterizations were done during or after the procedure.

Statistical Measures

Paired sample t test was used to compare the difference between pre- and post- treatment parameters. SPSS version 18 (IBM, Armonk, NY) was used for the statistical calculation.

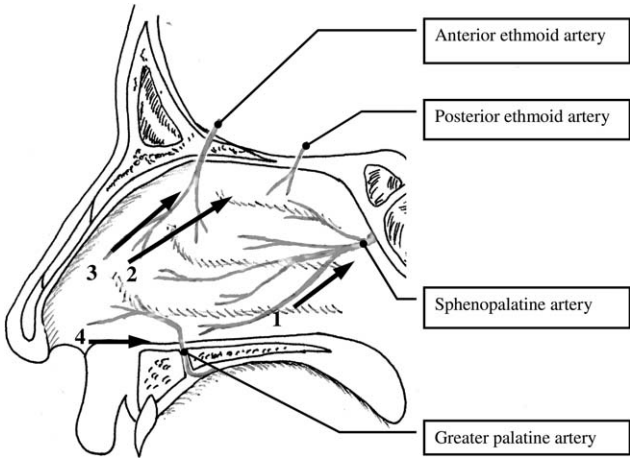

Fig. 1. Injection sites. (1) The sphenopalatine area. (2) Upper part of bony septum. (3) Upper part of the lateral nasal wall. (4) The anterior floor of the nose.

RESULTS

The effectiveness of the treatment was first evaluated 4 weeks after the treatment. Three of the eight patients did not respond to the bevacizumab injection, and two of these three received an additional treatment of the same dose 4 weeks after the first dose.

The mean time period from the first bevacizumab treatment until the last epistaxis severity evaluation was 9.5 weeks (range, 8–12 weeks; SD, 1.4). The mean pretherapy IFT epistaxis grade was 14.3 (range, 7–25; SD, 7.0). The mean post-therapy IFT epistaxis grade was 3.5 (range, 2–7; SD, 1.6). The difference between pretreatment and post-treatment IFT grading was statistically significant ($P = .007$).

The mean pretreatment ESS was 6.0 (range, 4.70–8.25; SD, 1.21). Post-therapy ESS average was 2.82 (range, 1.96–4.98; SD, 0.92). This difference in ESS was statistically significant ($P = .001$).

The mean pretreatment hemoglobin level was 10.6 g/dL (range, 8.4–13.2; SD, 1.6). The mean post-treatment hemoglobin level was 13 g/dL (range, 8.0–17.1; SD, 2.8) ($P = .01$). None of the patients received a blood transfusion after the treatment. No changes had been done to the dose of iron supplement therapy after the treatment except for patient 6, in whom the iron supplement was discontinued by the family doctor 4 weeks after the treatment because of the dramatic and rapid improvement in the hemoglobin level.

The effect of the therapy on HRQoL, measured by the SF-36 questionnaire, showed improvement in all SF-36 dimensions except bodily pain. These improvements were not statistically significant. In addition, there was an improvement in the mean overall QoL score and the disease-specific QoL, as shown in Table II. These improvements did not, however, reach statistical significance.

DISCUSSION

A wide variety of treatment options has been used for treating HHT-associated epistaxis (Table III).[5] All of these treatment options have some limitations and complications, and none of these options fit all patients. Therefore, new options are required. The new options should take into consideration other HHT-associated morbidities, such as pulmonary, hepatic, gastrointestinal, and nervous system involvement. For example, treatment options that require repeated general anesthesia are not suitable for patients with HHT-associated pulmonary complications.

During the last few years several groups have proposed intranasal administration of bevacizumab as a possible new treatment modality in HHT-associated epistaxis. Davidson et al.[18] published the first case report using intranasal bevacizumab injection and spray in local anesthesia for treating HHT-associated epistaxis. The authors concluded that intanasal bevacizumab could be a promising new treatment modality for HHT-associated epistaxis. Simonds et al.[14] treated 10 patients with KTP laser combined with intranasal injection of bevacizumab and nine patients with KTP laser alone, and found that the combined therapy significantly decreased the frequency of nosebleed and the need for blood transfusions, and improved QoL measured by work disability and social life improvements. Karnezis and Davidson[19] recently published their results of treating 32 HHT patients with intranasal bevacizumab, applied as either a topical spray or submucosal injection. They reported significant improvement in ESS after this treatment. The injections were done under general anesthesia. Chen et al.[17] found intranasal bevacizumab is safe in treating HHT-associated epistaxis.

Bevacizumab was administered following a standardized injection protocol, and we excluded the parallel use of additional treatments such as laser and cautery. The bevacizumab dose and the injection technique were standardized for all the patients. The technique is based on four injection sites corresponding to the points of entry of the main arteries responsible for the blood supply of the nasal mucosa: 1) the sphenopalatine area representing the entry point of the sphenopalatine

TABLE II.
Mean Pre- and Post-Treatment Quality of Life.

Health-Related QoL, SF-36	Before Treatment, n = 8	4 Weeks After Treatment, n = 8	*P* Value
Physical functioning	60.0	63.7	.080
Role physical	45.3	54.7	0.50
Bodily pain	71.1	70.0	0.90
General health	48.6	52.2	0.70
Vitality	36.9	45.0	0.30
Social functioning	62.5	67.2	0.88
Role emotional	45.0	56.7	0.30
Mental health	53.5	60.0	0.60
PCS	42.7	43.3	0.90
MCS	40.0	43.8	0.50
Overall QoL	5.8	6.8	0.20
Disease-specific QoL	6.3	6.0	0.40

PCS = Physical Component Summary; MCS = Mental Component Summary; QoL = quality of life; SF-36 = Short Form-36 Health Survey.

TABLE III.
Treatment Options for Hereditary Hemorrhagic Telangiectasia Associated-Epistaxis.

Cautery
Electro
Chemo
Cryo
Argon plasma
Hormonal
Topical
Estriol (estrogen)
Systemic
Tamoxifen (antiestrogen)
Estradiol
Medoxyprogesterone
Antifibrinolytic
Tranexamic acid
Ethamsylate
Surgical
Septodermoplasty
Closure of the nostril
Arterial ligation
Ethmoidal (anterior and posterior)
Maxillary
External carotid
Sphenopalatine
Selective arterial embolization
Laser
Argon
KTP
Nd-YAG
Diode
Pulsed dye
Anti-VEGF
Bevacizumab
Thalidomide
Radiotherapy (brachytherapy)

KTP = potassium titanyl phosphate; VEGF = vascular endothelial growth factor.

artery, 2) the upper part of the septum, 3) the lateral nasal wall representing the entry area of the anterior and posterior ethmoid artery, and 4) the anterior nasal floor covering the access point of the greater palatine artery (Fig. 1). Our hypothesis was that injecting bevacizumab in or near the entrance points of the vessels supplying blood would lead to more effective and more equal spreading of the drug to the whole nasal mucosa, thus resulting in an optimal therapeutic effect. Restricting the injections to four sites will make the procedure more suitable to being performed using local anesthesia and light sedation, even in patients with other HHT-related complications, because the risk of general anesthesia is avoided.

To evaluate the effectiveness of this treatment protocol, we used several objective and subjective measures. Hemoglobin levels were used as an objective measure. To measure the severity of epistaxis, the IFT grading system was used as an objective system. In addition, the ESS grading score was used, which represents a more subjective measure reflecting the patient's opinion about the severity of epistaxis.

Five of the eight patients showed good improvement after the first treatment, whereas three patients did not. For these, the severity of epistaxis, graded by the IFT and ESS systems prior to and 4 weeks after the first treatment, was unchanged (patient 3, 5, and 7 in Table I). Two out of these three patients received one more treatment after 4 weeks. The second dose was effective in both patients (Table I). The third patient (patient 7) has not yet received an additional dose.

Furthermore, we aimed to analyze QoL by three questionnaires of different levels in our evaluation: 1) overall QoL by CL questionnaire; 2) SF-36 questionnaire, which is a well-established tool in evaluating health-related QoL; and 3) Slotosch questionnaire for disease-specific QoL. Several studies have shown that epistaxis has the greatest impact on QoL in HHT patients.[3,6,29–33] However, other variables including sociodemographic characteristics (age, gender, marital status, employment status, and level of education), and disease-related characteristics (duration of illness, type of gene mutation, and the presence of other HHT manifestations like cerebral, pulmonary, gastrointestinal, and hepatic involvement) have significant impact on the QoL in HHT patients.[3,29,30,33,34] Almost all of the eight patients included in our study had other HHT complications (as mentioned in the Materials and Method section), such as pulmonary AVM, pulmonary hypertension, hepatic involvement, and gastrointestinal bleeding, which can affect the HRQoL negatively and make the HRQoL measures less sensitive for the improvement in epistaxis after the treatment. This can explain the lack of significant improvement in QoL after treatment in our study. On the other hand, generic QoL questionnaires have limited sensitivity, and a more clinically sensitive and responsive instrument for therapeutic evaluation in patients with epistaxis is missing.[30] Simonds et al.[14] used a QoL system measured by work disability and social life improvements to evaluate the effect of local bevacizumab treatment. Ingrand et al.[30] have newly introduced an epistaxis-specific QoL questionnaire as a complementary tool for treatment evaluation of HHT-associated epistaxis.

Only a few studies used HRQoL measured by the SF-36 questionnaire to evaluate the effectiveness of different treatment options of HHT-associated epistaxis.[6,31,35] Hitchings et al.[6] used the SF-36 to evaluate the effect of nasal closure (eight patients), argon laser (15 patients), and combination of argon laser and septodermoplasty (six patients) on HRQoL. Only the nasal closure group showed significant improvement in two of the eight dimensions of the SF-36 questionnaire 10 to 32 months after treatment. Karapantzos et al.[31] found a significant improvement in five out of eight dimensions of the SF-36 2 years after the first treatment of HHT-associated epistaxis with Nd:YAG laser in 27 patients. Jørgensen et al.[35] reported recently no

significant improvement in SF-36 score after laser coagulation therapy of nasal mucosa, but SF-36 scores before treatment were significantly lower than normative data in five out of eight dimensions, and the SF-36 scores were significantly lower than normative scores in two out of eight dimensions 6.5 months after the laser treatment.

In summary, five out of eight patients benefited significantly after a single treatment, whereas three did not. A variable individual sensitivity may mirror individual therapeutic resistance to bevacizumab. Therefore, it would be desirable for future studies to evaluate possible measures to predict the individual sensitivity pattern and to monitor the therapeutic response to bevacizumab. Monitoring the serum level of VEGF before and after the treatment with bevacizumab might be the first step in this evaluation.

All the included patients had been previously treated with diode laser, pulsed dye laser, and/or argon plasma coagulation. Although the aim of the study was not to compare the effectiveness of the previous treatment modalities with the currently described bevacizumab protocol, our impression is that the local therapy with bevacizumab may be of superior effectiveness. In this context, it is worth mentioning that a single bevacizumab injection is at the moment more expensive (costs in Norway: US$600/100 mg) than most of the other treatment modalities mentioned above, and it is unclear yet how often this treatment has to be repeated to gain comparable or better effect than the above-mentioned methods. Nevertheless, this has to be further evaluated in the future.

CONCLUSION

The short-term data from this prospective study identify bevacizumab applied by the four-injection site technique as an effective new treatment option in HHT-associated epistaxis. Nevertheless, long-term and comparative studies are needed to further evaluate the significance of this new treatment modality.

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