Intranasal submucosal bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: A double-blind, randomized, placebo-controlled trial

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ABSTRACT: *Background.* The purpose of this study was to investigate the efficacy of bevacizumab ("Avastin") for the treatment of epistaxis in hereditary hemorrhagic telangiectasia (HHT).

Methods. In this double blind, placebo controlled trial, 15 adult patients with HHT with a minimum of 2 epistaxis episodes per week were randomized. A history of thromboembolic events or recent or planned surgery led to exclusion. Patients received a single intranasal submucosal injection (10 mL) of 100 mg bevacizumab or placebo. The primary outcome was the relative reduction of average daily epistaxis visual analog score (VAS).

Results. Average daily posttreatment VAS scores decreased by 27% in the bevacizumab group and by 3% in the placebo group ($p = .57$). The reduction in HHT epistaxis severity scores was -0.61 greater in the bevacizumab group compared to the placebo group ($p = .34$).

Conclusion. Results show a trend toward reduced epistaxis with bevacizumab. This further supports the use of bevacizumab in HHT. Clincial Trials. gov number: NCT01314274 © 2014 Wiley Periodicals, Inc. *Head Neck* **37:** 783–787, 2015

KEY WORDS: Rendu–Osler–Weber syndrome, hereditary hemorrhagic telangiectasia (HHT), avastin

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease clinically diagnosed according to the Curacao criteria.[1] It leads to telangiectatic lesions of the mucous membranes of the nose, which result in recurrent epistaxis of varying degrees ranging from rare and short episodes to frequent and severe events necessitating red blood cell transfusions.

The treatment of epistaxis in HHT is a challenge and struggles with recurrent symptoms over time. One promising new treatment approach is bevacizumab, a monoclonal anti–vascular endothelial growth factor antibody. vascular endothelial growth factor plasma levels were shown to be about 15-fold elevated in patients with HHT[2] and bevacizumab use in patients has resulted in tremendous symptom relieve in case series when administered intravenously.[3] In order to reduce systemic side effects, local therapy of the nasal mucosa was described by Simonds et al[4] resulting in consecutive case series describing very promising success rates with intranasal submucosal and also consecutively with topical bevacizumab.[5]

The purpose of the present study was to establish the efficacy of a single dose of intranasal submucosal bevacizumab in a double blind, placebo-controlled trial.

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MATERIALS AND METHODS

Trial design

This was a single-center, double-blind, placebo-controlled, parallel-group study conducted in Vienna, Austria.

Eligibility criteria

Eligible patients were adult patients from 18 to 80 years of age diagnosed HHT, according to the Curacao criteria.[1] A minimum of 2 epistaxis episodes per week was required. Participants needed to be able and willing to participate. Patients were excluded with uncontrolled hypertension (systolic blood pressure >150 mm Hg), a history of a thromboembolic events, including myocardial infarction or a cerebral vascular accident. Malignancy of the upper respiratory tract within the last year, recent (<3 months) or planned surgery, proteinuria, or allergy to local anesthetic also excluded patients from participation. If nasal cautery or laser treatment was necessary in the 4-week pretreatment phase, patients were also excluded from randomization and treatment.

Setting

The study took place at the Department of Otorhinolaryngology, Head and Neck Surgery, at the Medical University of Vienna, Austria, a tertiary referral center.

Intervention

First, topical anesthesia and decongestion of the nasal mucosa with 4% lidocaine and ephedrine on medicated cotton wool, placed in the nose for 10 minutes, was applied. The study drug was injected into the nasal mucosa under endoscopic control using a 22-gauge spinal needle. Areas that were most affected by telangiectasias were predominantly infiltrated. The mucous membrane covering the cartilaginous septum was only infiltrated on one side to reduce the risk of septal perforation.

The study drug consisted of 100 mg of bevacizumab ("Avastin," Roche Pharma AG, Germany) in 10 mL NaCl (resulting in a concentration 10 mg/mL) or placebo (10 mL NaCl), 5 mL were injected into each side of the nose. Only 1 injection per participant was performed.

Follow-up visits were scheduled every 4 weeks up to the end of the observation period at 12 weeks posttreatment.

Outcome

Patients were instructed to use a diary in the month (days -28 to 0) before the intervention and in the 3 months after the intervention (days 10–84 postintervention). Patients filled out a daily visual analogue scale (VAS) to rate their overall epistaxis (Figure 1). The relation of the average daily posttreatment epistaxis VAS score (range, 0–100) compared to the average daily pretreatment score (R = VAS-post/VAS-pre) was considered the primary outcome. The first 10 days were not included in the analysis because a higher frequency of epistaxis was expected because of the treatment procedure in both groups. If nasal packing during the course of the study was necessary, VAS scores were set to a maximum of 100 for 3 consecutive days.

As secondary outcomes, patients noted the duration of daily epistaxis episodes. The epistaxis severity score[6] was also taken at each follow-up visit each month. Adverse events were also registered at each follow-up visit.

Sample size

At the beginning of the study, a clinically relevant relative reduction in average epistaxis VAS scores was considered to be 50% (ie, $R = 0.5$). Because the approximate variation of this outcome measure was not known, a sample size calculation was planned after an internal pilot of 15 completed patients. Using the data of this internal pilot to estimate the SD resulted in a required number of 31 patients per group with a power of 0.80 and a 2-sided p value of .05.

Because it was not possible to recruit such a high number of patients in this setting, the study was ended and analyzed at this point.

Randomization

A web-based randomization software program was used that randomly assigned treatment codes to each patient.

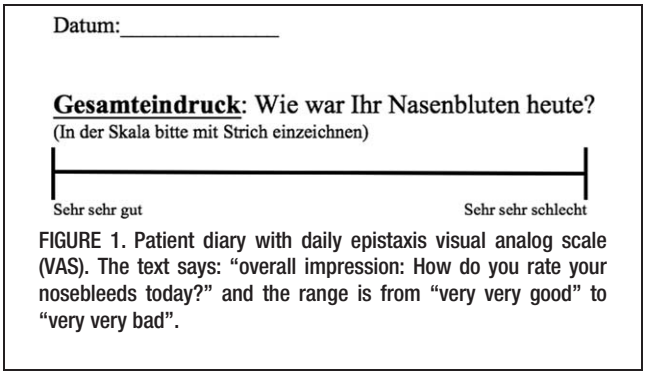

FIGURE 1. Patient diary with daily epistaxis visual analog scale (VAS). The text says: "overall impression: How do you rate your nosebleeds today?" and the range is from "very very good" to "very very bad".

Patients were stratified according to the 3 grades of frequency of epistaxis and according to 3 age groups. The treatment code was passed on to an independent pharmacist who, according to treatment code, prepared either the study drug or the placebo in identically labeled syringes. At the beginning of the study, a list with treatment codes and the corresponding assignment placebo versus bevacizumab was handed to the pharmacist by the data monitor. The investigators did not have any access to this list.

A random block size of 6 was used, but, because of the 2 stratification criteria and the low number of patients, this did not prevent an uneven random distribution in this study. Therefore, 9 patients were randomized by chance to the bevacizumab group and 6 patients to the placebo group.

Blinding

Patients and all investigators were blinded to treatment. Treatments were identical with the same amount of clear fluid. Labeling of syringes by the pharmacy was done with the computer-assigned treatment code. Data collection was also performed blinded.

Statistical methods

Because of the skew distribution of the primary outcome measure R (R = VAS-post/VAS-pre) log2-transformed values were used for statistical analyses. For description, re-transformed mean values and confidence limits are given. The unpaired t test was performed to test for statistically significant differences between the 2 treatment groups. All p values are results of 2-sided tests and p values $< .05$ were considered as indicating statistical significance.

RESULTS

Participant flow

Fifteen patients were randomized, received treatment, and were analyzed. To begin with, 25 patients with HHT were screened for enrollment. Seven did not meet the inclusion criteria (4 had too few episodes of epistaxis, 2 had a history of a thromboembolic event, 1 was too old, and 1 had upper respiratory tract malignancy) and 1 patient declined informed consent. Sixteen patients were enrolled into the study. One patient had no more episodes of epistaxis in the pretreatment phase and decided to drop out of the study before randomization, which resulted in a

TABLE 1. Demographic data of patients including average daily visual analog scale scores of epistaxis.

Group	Patient no.	Age, y	Sex	Pre-VAS	Post-VAS	Pre-ESS	Post-ESS
Bevacizumab	3	55	F	1.6	8.6	2.1	2.4
Bevacizumab	4	59	F	38.6	31.6	5.3	3.7
Bevacizumab	5	56	F	3.5	9.5	2.5	5.2
Bevacizumab	6	61	F	28.7	27.6	5.2	4.3
Bevacizumab	7	41	F	13.3	3.0	3.6	1.0
Bevacizumab	10	56	F	46.9	13.1	4.2	3.0
Bevacizumab	11	61	M	0.8	0.3	2.4	3.7
Bevacizumab	12	71	M	21.9	23.7	7.5	5.5
Bevacizumab	15	70	M	14.5	2.9	1.9	1.5
Placebo	1	76	M	27.1	34.2	4.4	5.5
Placebo	2	61	M	41.8	21.7	9.1	6.5
Placebo	8	66	F	13.5	15.2	3.9	3.2
Placebo	9	71	F	16.6	33.3	4.2	5.1
Placebo	14	56	F	2.1	2.3	3.3	3.4
Placebo	16	47	M	22.4	11.4	4.1	3.0

Abbreviations: VAS, visual analogue scale; ESS, epistaxis severity score.
Additionally, ESSs are also shown. Pre-values relate to the 1 month before treatment, and post-values relate to the 3 months after treatment.

total of 15 randomized patients. Of those 15 patients, there was no drop out and all patients were analyzed at the end of the study. Demographic data together with baseline characteristics are depicted in Table 1.

Visual analogue scale scores

Patients recorded in a diary their daily epistaxis VAS scores ranging from 0 (best situation) to 100 (worst case). Average daily VAS scores dropped from 18.8 (±16.5 SD) pretreatment to 13.4 (±11.6 SD) posttreatment in the bevacizumab group and from 20.5 (±13.4 SD) to 19.7 (±12.6 SD) in the placebo group. Absolute changes were not statistically significantly different ($p = .50$) between the 2 treatment groups and are depicted in Figure 2. The prespecified primary outcome, the relation of the average daily posttreatment VAS score compared to the average daily pretreatment score, did not show a statistically significant difference ($p = .57$). The mean relative reduction was 27% ($R = 0.73$; 95% confidence interval [CI], 0.30–1.75) in the bevacizumab group and 3% ($R = 0.97$; 95% CI, 0.55–1.71) in the placebo group.

Epistaxis severity scores

Epistaxis severity scores were recorded before the treatment and in the 3 months posttreatment at each follow-up visit. Scores dropped from 3.9 (±1.9 SD) to 2.9 (±1.4 SD) in the bevacizumab group and from 4.8 (±2.1 SD) to 4.5 (±1.5 SD) in the placebo group (Figure 3). The mean difference between groups was -0.61 (95% CI, -1.93 to 0.71) with a t test result of $p = .34$ indicating no statistically significant difference.

Duration of epistaxis episodes

Patients recorded the daily minutes of epistaxis in a diary. Average daily minutes across all intensities decreased from 6.2 (±5.2 SD) to 5.9 (±5.2 SD) in the bevacizumab group and increased from 12.8 (±14.5 SD) to 13.2 (±11.3 SD) in the placebo group (Figure 4). Statistical analysis with a t test revealed a mean difference of −0.53 (95% CI, −7.1 to 6.0), which was not statistically significant $p = .86$.

Adverse events

Overall, 6 patients, 3 in the placebo group and 3 in the bevacizumab group, reported a total of 12 adverse events during the study period. In the placebo group, a new onset of atrial fibrillation was noted. Massive muscle pain, neck pain, sleep disturbance, palpitations for several hours after treatment, burning pain in both temples for 10

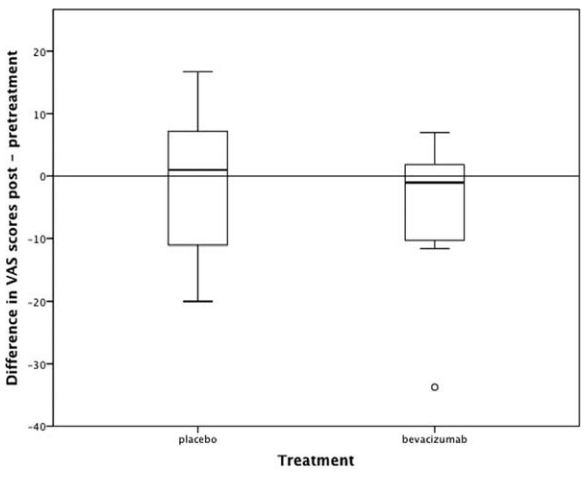

FIGURE 2. Box plots showing absolute changes in average daily epistaxis visual analog scale (VAS) scores in the bevacizumab and placebo group, respectively ($p = .50$). Statistical analysis of the primary outcome and relative changes revealed no statistically significant difference ($p = .57$). The boundaries of the box represent the 25th and 75th percentile, respectively. The line inside the box represents the median. The whiskers indicate the last measurement within 1.5 interquartile ranges from the 25th or 75th percentile, respectively. Circles represent values outside the box with a distance to the box of more than 1.5 times the box length.

days after treatment, and headaches in the mornings up to 2 weeks after treatment were reported in the placebo group. In the bevacizumab group, 1 patient reported an elevated blood pressure up to 170/124 mm Hg, which was treated by the primary physician and resolved. One event of rhinitis, 1 event of itching of the tip of the nose with a suspected herpes infection, and 1 event of tingling of the whole body for 3 days which started 1 week after treatment and resolved spontaneously, were all reported in the bevacizumab group. In addition, 1 patient in the bevacizumab group had an episode of serious epistaxis during the submucosal injection, which necessitated intermittent packing for 20 minutes before the injection could be resumed.

DISCUSSION

The present study is the first randomized controlled trial comparing intranasal submucosal bevacizumab to placebo in a double-blind setting. Results show a trend toward a reduced epistaxis VAS score. Also, the HHT epistaxis severity scores improved in the bevacizumab group. This is in accordance with previous case series of bevacizumab application in HHT.[4,7,8]

One limitation of the present study was that it was underpowered because of the high variation in epistaxis episodes within each patient even with placebo therapy. When planning the study, a greater and more consistent treatment effect was expected from the available case series and an internal pilot was planned, because the exact variation of the primary outcome was not known. After 15 patients, the variation was evaluated and resulted in a required overall number of 62 patients. Because there was no possibility to recruit that many patients, the study was ended and analyzed. This high variation of outcomes, even after placebo therapy, shows the necessity for controlled studies and needs to be kept in mind when reading case reports of treatment successes regarding epistaxis in the setting of HHT.

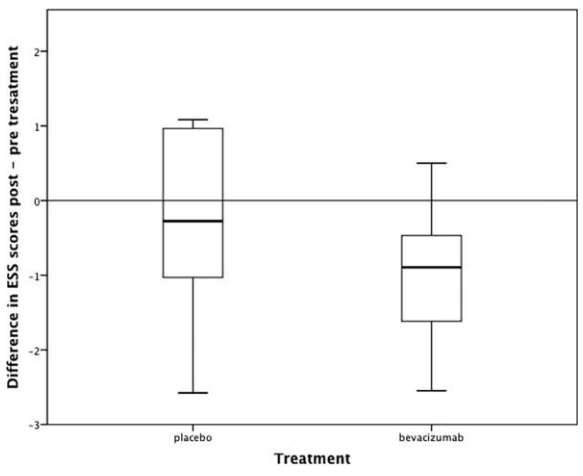

FIGURE 3. Box plots showing absolute changes hereditary hemorrhagic telangiectasia (HHT) epistaxis severity scores in the bevacizumab and placebo group, respectively. Statistical analysis revealed no statistically significant difference ($p = .34$). For details of boxplot parameters, see Figure 2 legend.

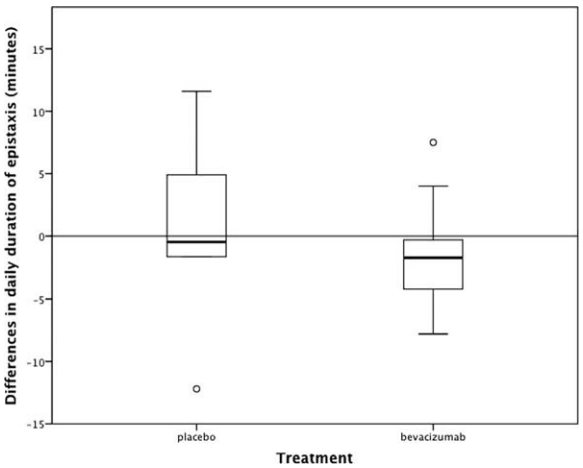

FIGURE 4. Box plots showing absolute differences in average daily overall duration of epistaxis in the bevacizumab group and the placebo group, respectively. Statistical analysis revealed no statistically significant difference ($p = .86$). For details of boxplot parameters, see Figure 2 legend.

This study set out to assess the efficacy of a single dose of intranasal submucosal bevacizumab over the 3 months after the intervention. As described by Karnezis and Davidson,[5] multiple doses are sometimes necessary to control epistaxis sufficiently. Also, in the study by Dheyauldeen et al,[8] 2 of the 8 patients treated with 100 mg of intranasal submucosal bevacizumab required a repeat treatment after 4 weeks. The lack of repeat injections in our protocol might have reduced the visible treatment effect of bevacizumab.

The strength of the present study was that it evaluated the effectiveness of bevacizumab for the first time in a controlled setting. This showed a high variability off epistaxis episodes in patients with HHT after placebo therapy. Therefore, larger, multicenter, controlled studies are needed to sufficiently prove the effect of an intervention in HHT.

Another important aspect of bevacizumab treatment is the evaluation of adverse events. Because intravenous application in oncologic patients showed an increased risk of thromboembolic events, gastrointestinal bleeding, and impaired wound healing, the local application of bevacizumab in patients with HHT was introduced.[4] A safety study in 52 patients[9] showed septal perforation as the only risk observed. These were all cases in which laser coagulation was used together with bevacizumab in the cartilaginous septum. In our patients, no septal perforations are reported. In order to reduce this risk, we only injected 1 side of the cartilaginous septum. One treatment-related event of serious epistaxis during intranasal injections was in a patient who had a very fragile nasal mucosa and needed red blood cell transfusions on a regular basis.

CONCLUSION

This study investigated the effect of intranasal submucosal bevacizumab on epistaxis in patients with HHT compared to placebo. Results show a trend toward reduced epistaxis with bevacizumab, albeit with no

statistical significance because of the high variation of epistaxis episodes within each patient. This randomized controlled trial supports the use of bevacizumab in the treatment of epistaxis in HHT.

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