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Injection of Bevacizumab and Cyanoacrylate Glue for Hereditary Hemorrhagic Telangiectasia

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Objectives/Hypothesis: The objective of this study was to report for the first time on the results of submucosal injections of bevacizumab used in conjunction with cyanoacrylate glue sclerotherapy in hereditary hemorrhagic telangiectasia (HHT).

Study Design: Retrospective analytic chart review.

Methods: We performed a chart review that included all patients with HHT treated with intranasal bevacizumab and cyanoacrylate glue for refractory epistaxis at Lariboisiere University Hospital from 2013 with a minimum follow-up of 6 months. We injected 100 mg (25 mg/mL) of bevacizumab diluted in 2 mL of serum at the base of the telangiectasias, and sclerotherapy with an injection of cyanoacrylate glue was used adjunctively. Treatment efficacy was based on changes in Epistaxis Severity Scores (ESS) and the Bergler-Sadick Scale. Quality of life and patient satisfaction were evaluated using the Cantril Self-Anchoring Ladder (CL) and Likert scale, respectively.

Results: Thirty-one patients were included, with a mean follow-up of 26.6 months. The average ESS score significantly decreased from 7.82 to 3.89 ($P < .05$). The Bergler-Sadick score significantly improved ($P < .05$) following the treatment, including the frequency (from 2.74 to 1.64) and the quantity (from 2.54 to 1.51) scales. Quality of life was significantly improved ($P < .05$) using the CL score (from 4.16 to 7.22). The Likert satisfaction scale related to the treatment efficacy was high, with an average of 7.03 out of 10. No complications were noted.

Conclusions: Submucosal injections of bevacizumab in conjunction with cyanoacrylate glue sclerotherapy significantly reduced epistaxis and improved the quality of life in HHT. Prospective comparative studies are needed to further evaluate the significance of this treatment modality.

Key Words: Hereditary hemorrhagic telangiectasia, bevacizumab, sclerotherapy, epistaxis, quality of life.

Level of Evidence: 3b

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant disease with incomplete penetrance and an associated incidence of 1:10,000.[1] The disease is also known as Osler-Rendu-Weber disease since it was first described in 1896 by Rendu, followed by reports by Osler in 1901 and Weber in 1907.[2] The diagnosis is based clinically on the criteria of Curaçao. At least three of the following four criteria are needed for the definite diagnosis of HHT: recurrent spontaneous epistaxis, evidence of mucocutaneous telangiectasias, positive first-degree relative history, and visceral arteriovenous malformations (AVMs).[3]

Mutations in the endoglin gene in HHT1 and ALK-1 gene in HHT2 lead to abnormal vascular formations, such as telangiectasias, which are small, dilated, and very fragile capillaries, or AVMs.[4] HHT1 is characterized by early epistaxis episodes and frequent pulmonary AVMs, whereas hepatic AVMs are more frequent in HHT2.[5] AVMs can develop in the liver, brain, lungs, or gastrointestinal tract and lead to serious complications.[6] However, epistaxis is the most frequent symptom that directly affects quality of life, with recurrent transfusions and restrictions in daily activities.[7] As telangiectasias becomes more prominent with time, epistaxis severity increases, with subsequent deterioration of quality of life.[8]

Currently, there is no curative treatment for HHT. Symptomatic treatments are needed repeatedly to reduce the frequency, volume, and severity of epistaxis and improve quality of life. Different treatment options are described in the literature, such as electrocoagulation, laser, tranexamic acid, radiofrequency, septodermoplasty, and Young's procedure, with varying success.[9] The use of sclerotherapy has also been described but only in retrospective studies. The optimal treatment is still debatable, but it should offer a long duration of action with few side effects.[10]

Angiodysplasia develops in HHT due to altered transforming growth factor-β (TGF-β) signaling during vascular development and hemostasis.[11,12] The reduction in TGF-β levels results in increased vascular endothelial growth factor (VEGF) levels. VEGF is an angiogenic factor that is highly elevated in the plasma of HHT patients.[13,14] VEGF induces proliferation and migration of endothelial cells resulting in immature vessel formation.[15] VEGF is a potential therapeutic target that plays a crucial role in HHT

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pathogenesis. Bevacizumab is a recombinant human monoclonal antibody that selectively inhibits VEGF.[16] There are few reports on topical bevacizumab used alone or in combination with other treatments in HHT with promising results.[17] We present the first series of HHT patients treated with a combination of submucosal bevacizumab injection (SBI) and cyanoacrylate glue sclerotherapy (CGS) for HHT-associated epistaxis.

MATERIALS AND METHODS

Patient Selection

We performed a retrospective, analytic chart review that included all patients with HHT treated for refractory epistaxis (defined as failure of conservative treatments such as anterior bidigital compression and anterior nasal packing) at Lariboisiere University Hospital in Paris from January 2013 to January 2018. Patients were included if they were older than 18 years, had HHT, were treated with a combination of SBI and CGS, and had a minimum follow-up of 6 months. Patients were excluded if they received at any time between baseline and last follow-up systemic bevacizumab or any other concomitant treatment (raloxifene or tamoxifene) that could reduce the severity of epistaxis.

Data Collection

The charts were retrospectively reviewed to obtain objective information such as the number of blood transfusions, hemoglobin levels, and the number and type of interventions. In addition, all selected patients were interviewed and completed two questionnaires for epistaxis evaluation before and after the treatment: the Epistaxis Severity Score (ESS) and the Bergler-Sadick Scale (BSS). ESS is a statistically validated score based on a comprehensive survey of a large cohort of HHT patients. It evaluates the frequency, duration, and severity of epistaxis, the need for medical interventions and blood transfusions, and the presence of anemia. Epistaxis is classified as mild for an ESS from 1 to 4, moderate from 4 to 7, and severe from 7 to 10.[18] The BSS focuses on the frequency and quantity of bleeding and is graded from 1 to 3.[19] In addition, the quality of life before and after the treatment was evaluated using the Cantril Self-Anchoring Ladder (CL).[20] The CL grades the general quality of life from 0 (low) to 10 (high). It is not specifically designed for HHT. Finally, the Likert scale was used to evaluate overall satisfaction with the treatment.[21]

Outcome Evaluation and Statistical Analysis

The primary outcome was a reduction in epistaxis severity as evaluated by the ESS and BSS. The secondary outcome was an improved quality of life as evaluated by the CL and the return to a functional daily activity level (social/leisure activity and professional activity for workers). The data were statistically analyzed using PASW 18.0 software (SPSS, Hong Kong). Paired-sample *t* tests were used to compare the difference between pre- and post-treatment parameters. Results with a P value <.05 were deemed significant.

Surgical Technique and Follow-up

The procedure was performed under general anesthesia. Gentle nasal packing was performed with cotton wool impregnated with 5% lidocaine and 0.02% naphazoline. The procedure was performed with a 30° nasal endoscope that revealed the extent of the telangiectasias in the nasal cavities (Fig. 1). First, 100 mg (25 mg/mL) of bevacizumab (Avastin) were diluted in 2 mL of serum, and a total of 3 mL (50 mg) were injected submucosally on each side (Fig. 2). Then, sclerotherapy was performed with injection of 1 mL of cyanoacrylate glue (Glubran 2) submucosally on each side (Fig. 3). The injections were performed at the base of the telangiectasias on the nasal septum and lateral nasal wall. Twenty-three–gauge needles were used for injection. In case of severe uncontrolled bleeding, resorbable Surgicel (Johnson & Johnson–Ethicon Endo-Surgery, Inc., Cincinnati, OH) was applied for nasal packing. Patients were evaluated 1 week after the procedure, at 1 month, at 6 months, and then every 6 months. Of note, a second injection was considered if the bleeding recurred at the same level as in the preoperative period. The postoperative time used to compare to baseline was the last follow-up: ESS, BSS, CL, and Likert scale scores were collected during the last follow-up visit.

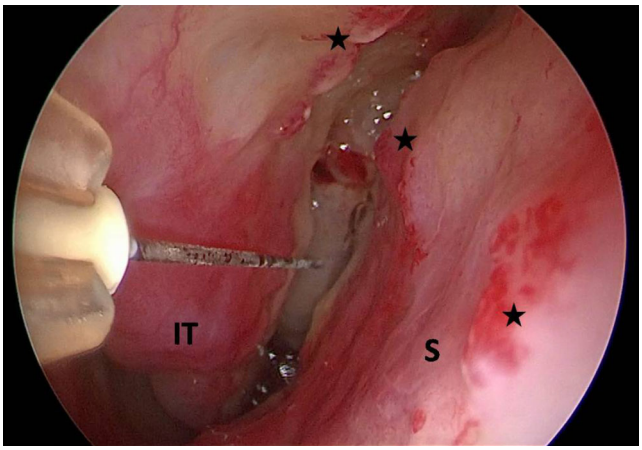

Fig. 1. Nasal endoscopy of right nasal cavity showing telangiectasias (black stars) on the lateral nasal wall superior to the inferior turbinate (IT) and the nasal septum (S).

RESULTS

Patients' Characteristics

A total of 31 patients were included for the study, with 16 females (51.6%) and 15 males (48.4%). The ages ranged

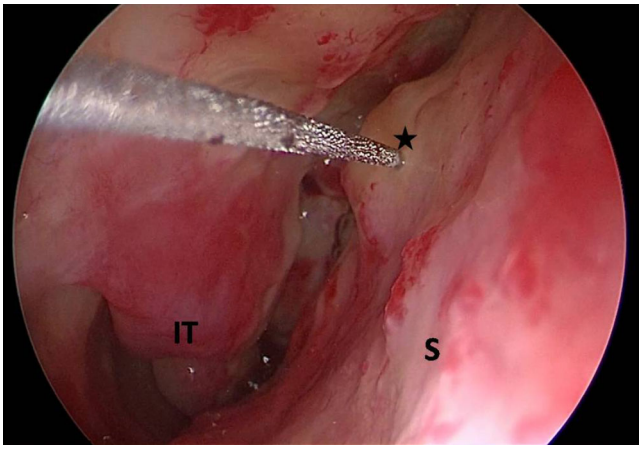

Fig. 2. Submucosal injection of bevacizumab at the base of a right septal telangiectasia (black stars). IT = inferior turbinate; S = nasal septum.

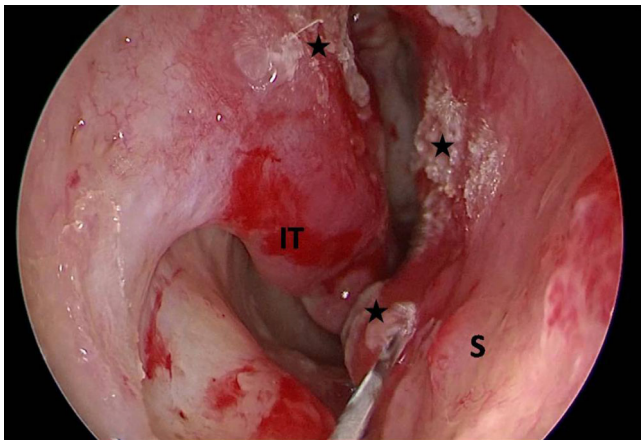

Fig. 3. Submucosal injection of cyanoacrylate glue at the base of right septal telangiectasias (black stars). IT = inferior turbinate; S = nasal septum.

from 36 to 83 years, with a mean of 60 years. Fourteen patients (45.2%) had high blood pressure, and four (13%) were taking blood thinners. Twenty-one patients (67.7%) had visceral involvement including the digestive tract, liver, pancreas, lungs, and brain (Table I). As mentioned in the exclusion criteria, none of the patients underwent any systemic treatment for HHT. Twenty-three patients (74.2%) received previous intervention under general anesthesia for HHT-related epistaxis. The types of previous interventions are summarized in Table II.

Treatment

The mean global follow-up period (between first injection and last follow-up) was 26.6 months (minimum = 9, maximum = 56). A total of 54 injections of bevacizumab (Avastin) with cyanoacrylate glue (Glubran 2) sclerotherapy were performed in 31 patients, with a mean of 1.7 injections and a median of 1 (minimum = 1, maximum = 5). The number of injections was distributed as follow: 17 (54.8%) patients had one, seven (22.6%) patients had two, six (19.4%) patients had three, and one (3.2%) patient had five. The mean period of time between injections was of 15 months (minimum = 4, maximum = 36). The mean period of time between the last injection and the last follow-up was 18 months (minimum = 6, maximum = 42).

TABLE I.
Patients' Characteristics.

	No. of Patients (%), N = 31
High blood pressure	14 (45.1%)
Blood thinners	4 (12.9%)
Visceral involvement	21 (67.7%)
Liver	12
Digestive tract	10
Lung	7
Pancreas	3
Brain	1

TABLE II.
Type of Previous Interventions for Hereditary Hemorrhagic Telangiectasia–Related Epistaxis.

	No. of Patients (%), N = 31
Previous interventions	23 (74.2%)
Cyanoacrylate glue sclerotherapy	16 (51.6%)
Electrocoagulation	5 (16.2%)
Embolization	1 (3.2%)
Radiofrequency	1 (3.2%)

During the procedure, severe bleeding requiring packing with resorbable Surgicel was noted in three of the 54 cases (5.5%). Two patients (3.7%) required blood transfusion due to an estimated blood loss of 1 liter. No postoperative complications were noted including septal perforation, severe crusting, or synechia formation.

Epistaxis Severity Evaluation

The average ESS score significantly decreased from 7.8 to 3.8 ($P < .05$) before and after treatment initiation (Fig. 4). Twenty-eight patients (90.3%) had a difference in ESS >0.71. This value was demonstrated as the minimal important difference (MID) significantly correlated with clinical improvement.[22] The proportion of severe epistaxis (ESS >7) significantly decreased from 77.4% to 9.7% ($P < .05$).

BSS also significantly improved ($P < .05$) following treatment initiation including the frequency of bleeding grading (from 2.7 to 1.6) and the quantity of bleeding grading (from 2.5 to 1.5) (Fig. 5). The proportion of severe epistaxis frequency (grade 3) significantly decreased from 77.4% to 12.9% ($P < .05$). The proportion of severe epistaxis quantity (grade 3) significantly decreased from 58.1% to 3.2% ($P < .05$). Table III summarizes the epistaxis severity outcome by grading. Hemoglobin levels could not be analyzed because data were missing in a significant proportion of the population. In addition, levels

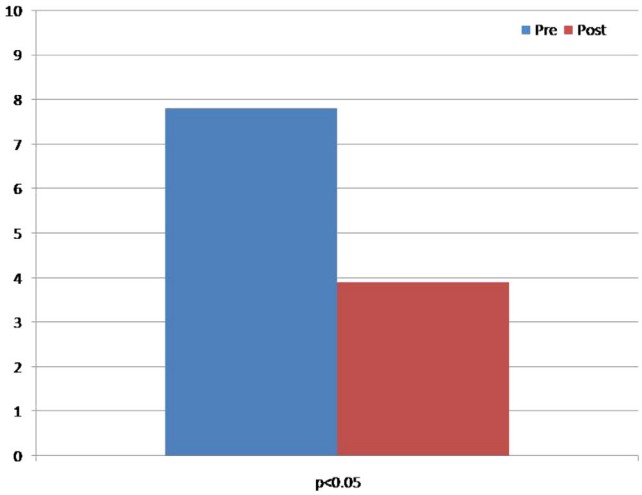

Fig. 4. Significant reduction of Epistaxis Severity Score following bevacizumab and glue injection.

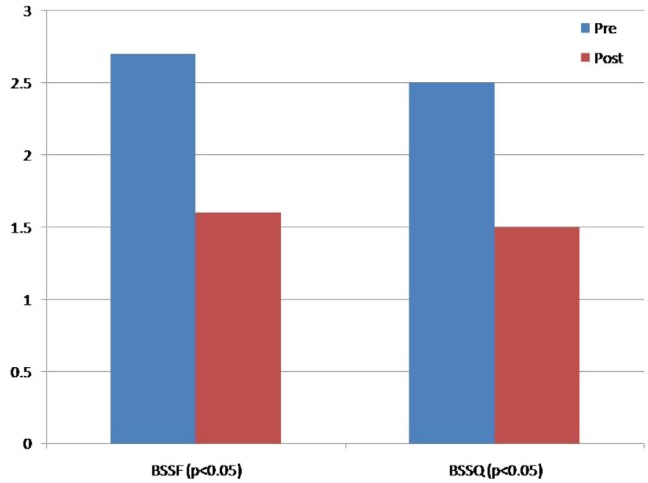

Fig. 5. Significant reduction of Bergler-Sadick Scale for Frequency (BSSF) and Bergler-Sadick Scale for Quantity (BSSQ) following bevacizumab and glue injection.

were occasionally measured following a recent blood transfusion.

Quality-of-Life Evaluation

Quality of life was significantly improved using the CL score, which increased from 4.1 to 7.2 ($P < .05$). Compared with before-treatment initiation, the quality of life was described as much better in 18 cases (58%), better in nine cases (29%), unchanged in four cases (13%), and worse in no cases (0%). Twenty-six patients (84%) noticed a significant improvement in their daily activity performance, whereas five (16%) did not experience any change. The Likert satisfaction scale related to the treatment efficacy was high, with an average of 7.03 out of 10.

DISCUSSION

Management of recurrent epistaxis is a major challenge given the lack of a curative treatment for HHT.[22] Multiple treatments are reported in the literature with variable outcomes.[23,24] Defining the best therapeutic option remains controversial. However, the best option should reduce epistaxis severity, improve quality of life, be repeated with the longest time interval, and be as minimally invasive as possible.[10]

Conservative therapy aims to moisturize the nasal cavity, thus reducing the probability of bleeding from a dry telangiectatic mucosa. The daily use of Vaseline ointment, mupirocin, or saline gels formulated with hyaluronic acid is recommended for this purpose,[25,26] whereas topical sesame oil/rose geranium oil therapy was proven to be efficient in one limited series.[27]

Multiple ablative techniques are described in the literature with variable success and complications rates. Monopolar electrocautery is associated with increased risk of septal perforation and crusting. Silver nitrate is not recommended due to imprecise cauterization and inefficiency in severe cases.[28,29] Bipolar electrocautery is generally preferred over monopolar electrocautery due to better precision and decreased depth of thermal injury, crusting, and risk of septal perforation.[30] Laser photocoagulation is also a popular option that offers the advantage of precise coagulation with relatively minimal depth of thermal injury and injury to the adjacent mucosa.[29] Argon laser, potassium titanyl phosphate (KTP) laser, and neodymium-doped yttrium aluminum garnet laser have been used with promising results. In general, laser fails to treat large conglomerate lesions, whereas smaller lesions are successfully treated.[19,31–33] Radiofrequency ablation of HHT-related telangiectasias is reported with a good success rate. This technique offers the advantage of deep ablation efficiency in large lesions with minimal surrounding thermal injury.[34,35] Septodermoplasty is an invasive but successful treatment that provides relatively long but not permanent remission, given that telangiectasias can later grow on the skin graft and on the lateral nasal wall.[24,36] Nasal closure or Young's procedure is an aggressive therapeutic option that can be reserved for severe refractory cases. It has a high definite success rate that should be balanced with the development of anosmia, changes in taste, nasal obstruction, and rare cases of life-threatening epistaxis that are difficult to control due to closed nasal vestibules.[37,38]

Recently, target therapies that potentially affect the pathophysiology of HHT-related vascular anomalies have been reported in the literature. Raloxifene and tamoxifene potentially increase of ALK-1 expression. Propranolol exerts an antiangiogenic effect and reduces VEGF expression.[21,39] Thalidomide can potentiate vessel maturation by stimulating pericyte and vascular smooth muscle cell formation.[40] These treatments were demonstrated to be efficient in limited studies.[15,21,41–44] However, their long-term use is limited by the risk of serious systemic side effects[24,45] and the increased risk of cancer in case of hormonotherapy.[33]

Bevacizumab is a growing therapeutic option for treating HHT. Bevacizumab is a recombinant human antibody selective toward all VEGF-A isomers with a half-life of 20 days.[20,46] Arizmendez et al. published a systematic review on the efficiency of intravenous (IV) bevacizumab in HHT.[47] The most frequent regimen was one dose every 2 weeks. Eighteen studies were included, with 14 focusing on epistaxis, and 13 of these studies were case reports

TABLE III.
Change in Epistaxis Severity Grading Following Bevacizumab and Glue Injection.

	ESS Mild	ESS Moderate	ESS Severe	BSSF (Grade 1)	BSSF (Grade 2)	BSSF (Grade3)	BSSQ (Grade 1)	BSSQ (Grade 2)	BSSQ (Grade 3)
Pre	0 (0%)	7 (22.6%)	24 (77.4%)	0 (0%)	7 (22.6%)	24 (77.4%)	1 (3.2%)	12 (38.7%)	18 (58.1%)
Post	19 (61.3%)	9 (23%)	3 (9.7%)	16 (51.6%)	11 (35.5%)	4 (12,9%)	16 (51.6%)	14 (45.2%)	1 (3.2%)

ESS = Epistaxis Severity Score; BSSF = Bergler-Sadick Scale for Frequency; BSSQ = Bergler-Sadick Scale for Quantity.

reporting improvement of epistaxis severity. Systemic benefits included improved cardiac and liver function. The main adverse events noted were hypertension, headache, nausea, abdominal pain, diarrhea, rash, and muscle pain. Given the need for frequent long-term injections and the potential of more serious complications, such as venous thrombosis and intestinal perforation, IV bevacizumab could be used to control visceral AVMs but not to exclusively target HHT-related epistaxis.[29]

To avoid the occurrence of serious systemic effects, topical bevacizumab was proposed with variable results depending on the route of administration, dosage, and combination therapy.[24–27] Intranasal sprays were ineffective in a well-conducted randomized controlled trial including 108 patients with HHT.[48] SBI is reported in a few small series with significant reduction of epistaxis severity.[9,16,20,49,50] One randomized controlled trial reported a trend toward improved outcome compared with placebo. However, significance was not attained because only 15 patients were included in the study.[51] In the study of Karnezis and Davidson, only 15 of the 32 included patients received SBI.[50] We report the largest series with 31 patients and the longest follow-up period (mean = 26.6 months). We used ESS to evaluate treatment efficacy because it is the only statistically validated patient questionnaire for HHT-related epistaxis based on a comprehensive survey of a large cohort of patients. It is a useful tool for evaluating treatment success and following nosebleed severity over time.[18] We also used the BSS to separately evaluate bleeding frequency and quantity.[19] The treatment was proven to be efficient, as there was a statistically significant reduction of both scores. Because there is no curative treatment for HHT-related epistaxis, we are interested in outcomes that indicate a significant improvement in the disease burden. One of these outcomes is the proportion of severe epistaxis (ESS >7) that significantly decreased from 77.4% to 9.7%. We also evaluated the proportion of patients who experienced a reduction of ESS >0.71, given that this value is considered as the MID significantly correlated to a clinical improvement.[22] We identified a proportion of 90.3% correlated to a high success rate. Finally, quality of life is a major outcome to be considered when treating HHT patients. We noted a significant improvement in the quality of life as evaluated by the CL score and the return to normal daily activity. In addition, it was previously demonstrated that the ESS is a major determinant of quality of life, and that a reduction in ESS is significantly correlated to improved quality of life measures.[52]

Given that bevacizumab has a limited half-life and there is still no curative treatment for HHT, patients will require repeated administrations for recurrent disease. In ophthalmology, bevacizumab is used to treat age-related macular degeneration and diabetic eye disease. Repeated injections are needed for disease control, and a tachyphylaxis regimen has been established with one injection every month. In HHT, a standard regimen has not yet been defined, and the treatment is repeated in case of recurrence.[50] In our study, the mean time period between injections was 15 months.

By blocking VEGF receptors, bevacizumab can inhibit the development of new telangiectasias with reduced effects on preexisting lesions. Therefore, for an optimal outcome, it would be better to combine SBI with an ablative method.[24] The studies that combined SBI with laser KTP or coblation radiofrequency[9,16,49] seem to have better results compared with those with SBI alone.[20,50,51] We report the first series that combines SBI with CGS. The use of glue is rarely reported in the literature.[10,53] When injected at the base of the telangiectasias, it induces an inflammatory reaction, acting similar to a sclerosing agent. This combination offers the advantage of avoiding any thermal injury to the mucosa with minimal crusting and optimal mucosal function preservation. In addition, the glue could locally retain the injected bevacizumab with the potential for prolonged and more efficient activity.

SBI is a safe procedure, and only one case of a systemic adverse event is reported in the literature.[54] Few cases of septal perforation are reported when bevacizumab was injected in the nasal septum.[16,55] Injection of the nasal septum was not further recommended to avoid this complication.[50] A four-site injection protocol at the entry point of the main nasal arteries was also recommended.[20] In our study, no cases of septal perforation were noted, even though the nasal septum was bilaterally injected. We believe that the cases reported were related to the concomitant laser application.[16,55] In the absence of thermal injury with the cyanoacrylate glue sclerotherapy, the risk of septal perforation may be significantly reduced.

Our study has several limitations. The most important is probably the lack of a control group. Other studies on HHT have demonstrated that however promising the results of a therapeutic strategy may look, they may not be confirmed by controlled studies.[56,57] As this was a retrospective study with a relatively low number of patients, no statistical power and necessary sample size could be calculated. Finally, the number of injections was not the same for all patients, making it difficult to accurately compare the results. We chose to base our assessment on the results of the last-follow-up. As a consequence, the postoperative time used to compare to baseline was heterogeneous, and ranged from 6 to 42 months after the last procedure.

CONCLUSION

SBI combined with CGS has promising results for HHT-related epistaxis. It offers the advantages of targeting the pathophysiology of the disease while being safe, noninvasive, and repeated with a relatively long time interval. Further comparative studies are needed to define the best therapeutic option with a standard regimen in the absence of any curative therapy.

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