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Sclerotherapy Versus Cautery/Laser Treatment for Epistaxis in Hereditary Hemorrhagic Telangiectasia

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Objectives/Hypothesis: Surgical interventions for epistaxis management in hereditary hemorrhagic telangiectasia (HHT) demonstrate short-term success and require repeated procedures for disease control. Although electrocautery and/or laser photocoagulation (C ± L) are most frequently performed, sodium tetradecyl sclerotherapy (STS) is emerging as a promising newer treatment. We hypothesized that in a 24-month time period, STS would require fewer treatments than C ± L to maintain epistaxis severity within the mild range.

Study Design: Retrospective study.

Methods: We retrospectively assessed 67 patients with HHT with moderate and severe epistaxis that were treated periodically with C ± L (34 patients) versus STS (33 patients). The primary outcome was the number of procedures needed to maintain the epistaxis severity score (ESS) as mild. Secondary outcomes assessed for differences in postoperative complications, hemoglobin levels, iron stores, hematologic support, and quality-of-life (QoL) scores.

Results: To maintain ESS in the mild range, 1.6 STS procedures (range, 1–4) were performed versus 3.6 C ± L procedures (range, 1–8) ($P = .003$). Significant postoperative differences included reduction in nasal crusting (3% vs. 32%, $P = .001$), foul odor (3% vs. 35%, $P < .001$), and septal perforation (3% vs. 29%, $P = .006$) after STS. There were no significant differences between the two treatments in hemoglobin levels, iron stores, hematologic support, or QoL scores.

Conclusion: STS is able to attain satisfactory epistaxis control with significantly fewer procedures and lower postoperative complications than C ± L. STS should be considered as the initial surgical intervention for epistaxis in patients with HHT.

Key Words: Hereditary hemorrhagic telangiectasia (HHT), epistaxis, sclerotherapy, electrocautery, laser photocoagulation, septal perforation.

Level of Evidence: 4

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant vascular disorder that affects approximately 1 in 5,000 individuals and is characterized by dysplasia of large vessels that include arteriovenous malformations (AVMs) and of small vessels that include telangiectasias.[1] Various causative mutations, all involved in the signaling cascades of angiogenesis, have been identified, but the vast majority of cases encountered in clinical practice are due to haploinsufficiency mutations within *ENG* and *ACVRL1*.[2,3] Telangiectasias of the nose are the most common manifestation of HHT and predisposes patients toward recurrent epistaxis.[1,4] This is often the presenting symptom and over 95% of patients experience episodes of epistaxis at some point in their lifetime.[4,5]

Epistaxis severity usually worsens with advancing age and can be measured objectively using a 10-point standardized scoring system, the epistaxis severity score (ESS), with higher scores reflective of more severe bleeding.[6,7] Chronic nasal hemorrhage causes significant morbidity and increases mortality in HHT.[8,9] Among the various clinical manifestations of HHT, recurrent epistaxis has the greatest negative impact on patient quality-of-life (QoL) measures.[9]

An incremental approach is usually recommended for the management of epistaxis in HHT and is based on the ESS.[6,10] For patients with mild disease (ESS <4), treatments focus on various emollients for moisturization and on saline sprays for humidification of the nasal passages to maintain mucosal integrity.[1,6] For patients with moderate (ESS ≥4 to <7) and severe (≥7) diseases, various surgical procedures have been performed.[10,11] The initial operations most commonly performed include bipolar electrocautery and laser photocoagulation with potassium titanyl phosphate or neodymium-doped yttrium aluminum garnet.[12,13] Although proven beneficial, limitations to these treatments include the need for repeated treatments and cumulative risks of thermal injury to surrounding mucosal tissue.[10] Advanced surgical options including septal dermoplasty and complete nasal closure

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with the Young's procedure are usually reserved for refractory cases that have inadequately responded to initial interventions.[10,11] While highly effective, these advanced procedures can be associated with disadvantages of nasal crusting, foul odor, obligate mouth breathing, anosmia, hypogeusia, the unquestionable return of epistaxis with septal dermoplasty, and the rare but life-threatening loss of ability to acutely pack the nose should epistaxis return with the Young's procedure.[11]

Another intervention, sodium tetradecyl sclerotherapy (STS), wherein angiodysplastic lesions are injected to induce sclerosis and collapse of the vessel wall, has been shown to be safe and effective in reducing the severity of nasal bleeding in HHT.[14] Recently, Boyer et al. published a prospective randomized crossover trial that demonstrated the superiority of sclerotherapy over electrocautery in a short-term interval of 6 weeks.[15] Besides this study, there is a paucity of long-term efficacy and safety data regarding STS in the treatment of HHT-related epistaxis. Also, none of these aforementioned surgical procedures are curative and in the majority of patients, multiple treatment sessions are needed over the years to maintain ESS within the mild range.[1,11]

We therefore sought to compare the number of procedures needed in a 24-month time period to maintain epistaxis severity within the mild range in patients with HHT undergoing STS versus those undergoing bipolar electrocautery and/or laser photocoagulation (C $\pm$ L) and hypothesized that STS would require fewer treatments.

METHODS

Study Population

Prior to beginning this retrospective study, approval was obtained from the Institutional Review Board. A computer-assisted search was performed to identify adult cases (≥18-years of age) with a history of definite HHT as defined by the Curaçao criteria that were assessed for epistaxis at our institution.[16] Patients that had undergone C $\pm$ L and STS as the surgical procedure(s) for management of moderate and severe recurrent epistaxis (ESS ≥4) and had follow-up for a 24-month period over a time frame from January 01, 2014, to December 31, 2019, were included.

As a tertiary referral center, patients are often referred for comprehensive HHT care to our Center of Excellence (COE) and their epistaxis is periodically managed by local otolaryngologists. From this referral group, 34 patients that had undergone initial surgical interventions with C $\pm$ L were selected as long as details of their procedures and follow-up data over a duration of 24-months were available. Since HHT is a rare disease, heterogeneity in epistaxis care can arise if these referral patients are managed by an otolaryngologist in private practice that intervenes only on a handful of patients when compared to those managed by surgeons at an HHT COE with a larger patient volume and higher technical skill level. To avoid this heterogeneity, we analyzed the number of interventions performed on 20 patients (59%) managed by private otolaryngologists and on 14 (41%) by surgeons at an HHT COE. There was no significant difference between the 3.5 procedures (range, 2–8; cumulative total = 70) performed by otolaryngologists in private practice compared to 3.8 procedures (range, 1–6; cumulative total = 53) performed at an HHT COE ($P = .732$) over the 24-month time period. Thirty-three patients that had been treated with STS at our COE and had follow-up duration of at least 24 months were also selected. Within this group were 24 patients (73%) who were naive to any surgical intervention and 9 patients (27%) who were previously managed with C $\pm$ L.

Patients that had undergone other surgical operations including septal dermoplasty, Young's procedure, arterial embolization, and submucosal bevacizumab injection prior to consideration for STS or C $\pm$ L were excluded. Patients who underwent surgical interventions for mild epistaxis as defined by an ESS <4 were not included. Finally, patients being evaluated for a surgical intervention while on systemic antiangiogenic therapies including bevacizumab, pazopanib, thalidomide, and pomalidomide were also excluded.

The primary outcome measure was to assess the number of procedures needed to maintain epistaxis severity within the mild range (ESS <4). Secondary outcomes assessed for significant differences between these two treatment cohorts with regard to postoperative complications, hemoglobin levels, iron stores, and the need for hematologic support with blood transfusions and/or intravenous iron infusions. All patients had follow-up clinical visits with vital signs, laboratory evaluations for complete blood counts, serum ferritin, iron and transferrin saturation, and ESS calculations at baseline and at every 6-month interval. The ESS score, hemoglobin levels, and iron stores and need for hematologic support were compared at baseline and at each 12-month interval between the two treatment cohorts. Since more than one value was measured in the 12-month time period, the average value was documented for statistical analysis.

QoL information was collected by administering the 12-Item Short Form Health Survey (SF-12) at the end of the 24-month period and included recall of baseline values, and the results obtained were compared between the two treatment cohorts. Postoperative complications collected within 30 days after surgery included subjective reporting of nasal crusting, nasal/facial pain, foul odor, paradoxical worsening of epistaxis as defined by an increase in the ESS by ≥0.71, and endoscopic evidence of septal perforation.

Sclerotherapy Technique

The sclerotherapy technique performed in this study was a modified version of the technique described by Boyer et al.[15] All procedures were performed under general anesthesia in the operating room and none were performed in the office setting to address all telangiectasias at one treatment setting, including the ones located posteriorly in the nasal cavity that may not be amenable to treatment in the office location. Patients' nasal cavities were initially sprayed with oxymetazoline after orotracheal intubation. Next, 1% lidocaine with 1/100,000 of epinephrine was injected submucosally into both nasal septa, middle and inferior turbinates, and the lateral nasal wall. Complete visualization of telangiectasias within the nasal cavities was achieved by removing dried blood with a mixture of 50% hydrogen peroxide and 50% saline solution.

Using a 4:1 ratio of air to 3% sodium tetradecyl sulfate, the solution was foamed and injected into each lesion with a 25-gauge needle. Care was given to insert the needle only 1 to 2 mm submucosally and to inject until blanching of the surrounding mucosa was seen. Preference was to begin the injection in the posterior portion of the nasal cavity and progress anteriorly. This maneuver prevented any bleeding created by the injection from impairing visualization of subsequent lesions. After injecting all visible lesions in one nasal cavity, this process was repeated on the contralateral side in identical manner. Amounts of solution injected varied from patient to patient depending on the number and size of lesions, but the total volume injected did not exceed 3 ml per session. Once completed, the nose was rinsed with saline and the nasal cavity was filled with bacitracin ointment.

Bipolar Electrocautery and Laser Photocoagulation

Sessions of C ± L were performed in standard manner and this was conducted under general anesthesia in the operating room in 109 sessions (89%) and with local and topical anesthesia in the office for 14 procedures (11%). These 14 office-based procedures were conducted in 12 patients (35%), all of whom had additional procedures performed in the operating room over the 24-month period, and none of these patients were managed exclusively with interventions done under local and/or topical anesthesia.

Statistical Analysis

The information collected on the patients was described using counts, means, standard deviations, medians, quartiles, and ranges for all continuous variables and counts and percentages for all categorical variables. We applied the Wilcoxon rank-sum test to evaluate whether the number of treatments were significantly different between STS and C ± L. Significant differences between the two treatment groups were also assessed using Fisher's exact test and Chi-square test on categorical variables while the Wilcoxon rank-sum test was used on continuous variables. Generalized linear mixed models were used to assess for differences in hemoglobin levels, iron counts, and need for hematologic support over the 24-month period. All analyses were two-tailed and were performed at a significance level of 0.05, and were determined using the SAS 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

The median age of the 67 patients was 51 years (range: 36–71) and 58% were female. Table I lists the demographic and baseline characteristics of all patients at the time of surgical intervention. Genetic analysis revealed pathogenic mutations in *ACVRL1* in 36 patients (54%), *ENG* in 21 (31%), and *SMAD4* in 4 (6%) and 6 (9%) either had no identifiable mutations or did not undergo genetic testing. There was no significant difference in the distribution of mutations between the two treatment groups ($P = .797$).

The mean ESS at baseline was 6.46 (range: 4.24–9.49) of the entire cohort, with 20 patients (30%) having severe epistaxis and 47 (70%) with moderate disease. The mean ESS in those with moderate epistaxis was 5.98 (range: 4.24–6.84) and was 7.82 (range: 7.07–9.49) in those with severe disease. There was no significant difference between the two treatment groups with regard to the severity of epistaxis as shown in Table I.

As shown in Figure 1, both treatments were able to reduce and maintain the ESS within the mild range (<4) in the majority of patients at the end of the 24-month period. This goal was achieved in 28 patients (85%) with STS and 28 patients (82%) with C ± L ($P = .876$). A cumulative total of 54 procedures were performed in the STS cohort, while 123 procedures were conducted in the C ± L cohort ($P = .003$). The latter cohort included 52 sessions (42%) of laser photocoagulation, 46 (37%) of electrocautery, and 25 procedures (20%) that included both treatment modalities. To maintain ESS in the mild range as displayed in Figure 2, 1.6 STS procedures (range, 1–4) were performed compared to 3.6 C ± L

Table I.
Baseline Characteristics of Patients With HHT at Time of Initial Surgical Intervention With Either Electrocautery and/or Laser Photocoagulation (C ± L) and Sclerotherapy (STS).

Variable	C ± L (n = 34)	STS (n = 33)	*P* Value
Age	52.2 ± 8.3	50.1 ± 8.3	.303
Male	15 (44%)	13 (39%)	.653
Female	19 (56%)	20 (61%)	.752
Smoking history	10 (29%)	7 (21%)	.606
Pulmonary AVMs	14 (41%)	12 (36%)	.816
Brain vascular malformations	2 (6%)	4 (12%)	.079
Chronic GI bleeding	6 (18%)	10 (30%)	.149
Hepatic vascular malformations	10 (29%)	11 (33%)	.621
ESS	6.24 ± 1.48	6.68 ± 1.24	.653
Moderate epistaxis	26 (76%)	21 (64%)	.562
Severe epistaxis	8 (24%)	12 (36%)	.341
Hemoglobin (g/dl)	11.7 ± 1.2	11.9 ± 1.3	.575
Ferritin (ng/ml)	113 ± 46	105 ± 40	.342
TIBC (μg/dl)	394 ± 156	402 ± 135	.476
Iron (μg/dl)	75 ± 37	56 ± 32	.412
IV iron infusions	22 (65%)	18 (55%)	.241
RBC transfusions	10 (29%)	8 (24%)	.838
SF-12 PCS	38.01 ± 11.9	37.63 ± 13.4	.862
SF-12 MCS	39.17 ± 11.8	43.66 ± 6.3	.457

AVM = arteriovenous malformation; ESS = epistaxis severity score; HHT = hereditary hemorrhagic telangiectasia; TIBC = total iron binding capacity.

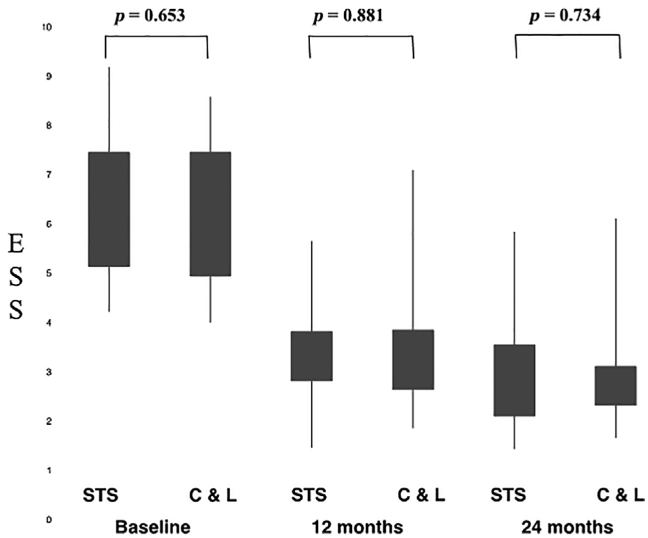

Fig. 1. Epistaxis severity score (ESS) in patients treated with electrocautery and/or laser photocoagulation (C & L) versus sclerotherapy (STS) over 24-month period. ESSs improved and were maintained at mild (<4) levels in both groups with no significant differences between the two groups.

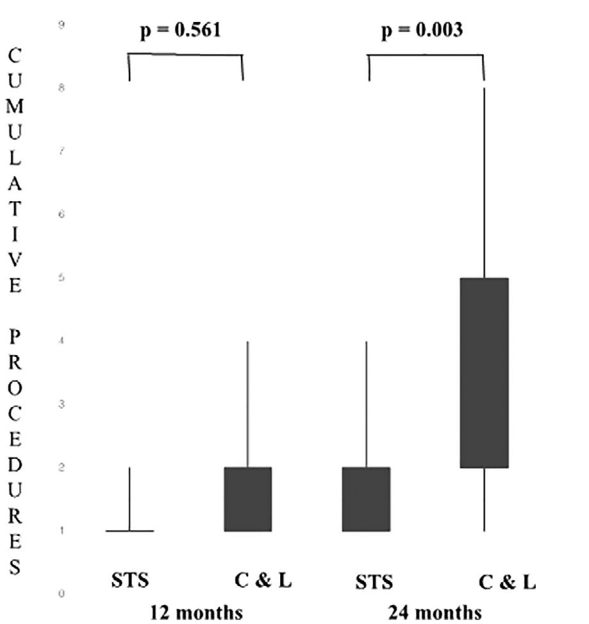

Fig. 2. Cumulative number of procedures performed to maintain epistaxis severity score (ESS) at mild (<4) levels in patients undergoing sclerotherapy (STS) versus electrocautery and/or laser photocoagulation (C & L) over a 24-month period. C & L required significantly more treatments than STS.

procedures (range, 1–8), (P = .003). The majority of patients (57 patients [85%]) required ≤4 interventions over the 24-month period and the distribution of patients with respect to the number of procedures is displayed in Figure 3.

The most common postoperative complication was nasal and facial pain, noted in 17 patients (25%) with no significant difference noted between the two groups. All

Fig. 3. Distribution of patients according to the number of sclerotherapy versus cautery and/or laser treatment procedures performed at the end of the 24-month period to maintain epistaxis severity score (ESS) at mild (<4) levels.

Table II.
Postoperative Complications for Patients With Hereditary Hemorrhagic Telangiectasia and Moderate-to-Severe Epistaxis Treated With Surgical Intervention of Electrocautery and/or Laser Photocoagulation (C ± L) Versus Sclerotherapy (STS).

Variable	C ± L (n = 34)	STS (n = 33)	*P* Value
Nasal crusting	12 (35%)	1 (3%)	**<.001**
Nasal/facial pain	8 (24%)	9 (27%)	.746
Septal perforation	10 (29%)	2 (6%)	**.006**
Foul odor	11 (32%)	1 (3%)	**.001**
Worsening epistaxis	5 (15%)	1 (3%)	.057

Bold values are statistically significant *p* values.

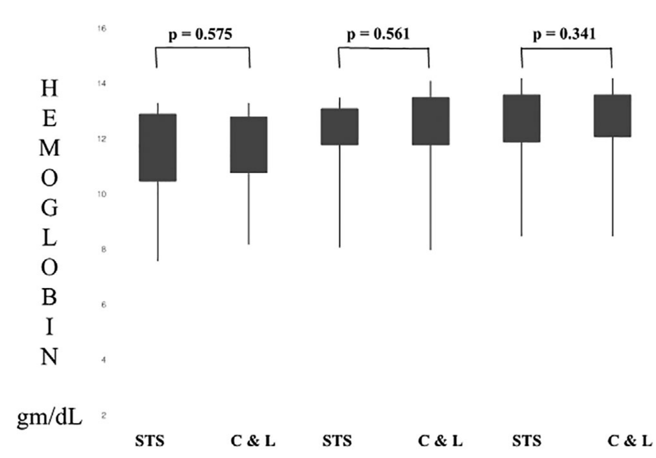

Fig. 4. Hemoglobin levels in patients treated with sclerotherapy (STS) or electrocautery and/or laser photocoagulation (C & L) over a 24-month period.

other postoperative complications are shown in Table II. There were significantly lower rates of foul odor (3% vs. 32%, P = .001), nasal crusting (3% vs. 35%, P < .001), and

Table III.
Outcomes for Patients with HHT and Moderate to Severe Epistaxis Treated With Surgical Intervention of Electrocautery and/or Laser Photocoagulation (C ± L) Versus Sclerotherapy (STS).

	12-Months			24-Months		
Variable	C ± L (n = 34)	STS (n = 33)	*P* Value	C ± L (n = 34)	STS (n = 33)	*P* Value
ESS	3.45 ± 0.61	3.34 ± 0.76	.881	2.72 ± 0.34	2.78 ± 0.52	.734
Hemoglobin	12.4 ± 1.3	12.5 ± 1.3	.561	12.9 ± 0.9	12.8 ± 1.1	.341
Ferritin	125 ± 28	142 ± 36	.258	145 ± 22	156 ± 47	.477
TIBC	326 ± 149	318 ± 102	.687	297 ± 89	311 ± 112	.241
Iron	95 ± 37	81 ± 34	.507	98 ± 28	86 ± 37	.734
IV iron infusions	15 (44%)	12 (36%)	.692	12 (35%)	11 (33%)	.816
PRBC transfusions	7 (20%)	6 (18%)	.727	2 (6%)	4 (12%)	.279
SF-12 PCS	ND	ND		54.29 ± 3.2	51.75 ± 0.7	.353
SF-12 MCS	ND	ND		49.94 ± 0.1	49.74 ± 0.3	.962
No. of procedures	1.1 (1–2)	1.6 (1–4)	.561	1.6 (1–4)	3.6 (1–8)	**.003**

Bold values are statistically significant *p* values.
ESS = epistaxis severity score; TIBC = total iron binding capacity; PRBC = packed red blood cells.

septal perforation with STS (3% vs. 29%, $P = .006$), as well as a nonsignificant trend toward less paradoxical worsening of epistaxis after STS (3% vs. 15%, $P = .057$). None of the patients in either group experienced serious adverse events of permanent or transient visual loss or focal neurological deficits on postoperative follow-up.

The median hemoglobin of the entire cohort was 11.8 g/dl at the beginning of the study with no significant difference between the two cohorts throughout the study period as shown in Figure 4. There were also no significant differences in measures of iron stores including ferritin, total iron-binding capacity, and iron levels over time as shown in Table III. All patients were receiving oral iron supplementation, 40 patients (60%) received periodic infusions of IV iron, and 18 patients (27%) had received ≥2 units of blood within 6 months prior to surgical intervention. As displayed in Table III, both treatment arms reduced needs for hematologic support, but there were no significant differences between the two surgical interventions in their effects on reducing IV iron infusions ($P = .816$) and blood transfusions ($P = .279$). Both treatment arms significantly improved the physical composite summary (PCS) and mental composite summary (MCS) of the SF-12 score at the end of the 24-month period (PCS: 37.82 ± 12.7 vs. 53.02 ± 1.9, $P = .023$, MCS: 41.45 ± 9.1 vs. 49.84 ± 0.2, $P = .047$), but there was again no significant difference between the two treatment groups with respect to the extent of improvements in QoL scores as displayed in Table III.

DISCUSSION

This long-term retrospective study demonstrates that STS is effective in reducing epistaxis associated with HHT. Not only did this study demonstrate that the number of procedures required to keep the ESS within the mild range is significantly less than that of C ± L, but it also resulted in fewer postoperative complications. From our perspective, the most important significance was that STS resulted in lower rates of nasoseptal perforation. There is evidence that the risk of developing septal perforation is associated with the depth of mucosal injury.[17,18] With STS, sclerosis is limited to the superficial mucosal vessels as opposed to C ± L, wherein there is fibrinoid necrosis to the deeper submucosal vessels from the penetrant thermal injury,[18] and this likely influences the lower rates of septal perforation with STS. This is a favorable finding because septal perforations often result in turbulent air flow within the nasal cavity that contribute to mucosal drying and nasal crusting, which predisposes to increased episodes of epistaxis.[19] This study also demonstrated a significantly lower rate of foul odor, nasal crusting with scabs, and a trend toward less postoperative paradoxical increase in bleeding. This is not surprising because in contrast to C ± L, STS does not result in any thermal damage to the surrounding mucosa with resultant sequelae of scab formation.[10,12]

The seminal study by Park et al. demonstrated that physiological and/or environmental factors that induced mucosal wounding in the presence of a genetically predisposed Alk1-deficient mouse were sufficient to trigger a dysplastic angiogenic environment to facilitate the formation of AVMs.[20] The results from this study provide clinical insights relevant to understanding the pathobiology behind telangiectasia formation in the nose. The trend toward less paradoxical worsening of epistaxis and the fewer procedures needed with sclerotherapy over 24 months in this study suggests that the benefits of sclerotherapy over C ± L laser may stem from the lack of thermal mucosal wounding resulting in less dysplastic angiogenesis during healing.

Despite an increasing awareness of HHT in the otolaryngology community, there is a paucity of literature regarding the comparative and long-term effects of STS. Boyer et al published a prospective randomized crossover trial that demonstrated the superiority of sclerotherapy over electrocautery in a short-term interval of 6 weeks.[15] The current study, despite its retrospective design, adds to data on the long-term (24 months) benefit of STS when compared to current standards of therapy, including $C \pm L$. This study is significant because it is the first to quantify the number of procedures required to maintain patients with moderate-to-severe HHT within the mild range of the ESS and showed that STS was able to accomplish this with significantly fewer treatment sessions. The results of this study are generalizable and represent patients with HHT seen in other clinical practices.[13,15] For example, Harvey et al. reported that patients with an average hemoglobin of 11.75 g/dl required more than three procedures over a prolonged period for satisfactory disease control, as was reflected in this series.[21]

This study has limitations, however. This is the reported experience at a single center and is retrospective in nature, and a referral bias is inherent given that the study was of a population presenting to a tertiary care center. However, this study is strengthened by the well-characterized nature of the patients and is bolstered by how well the represented cohort pathophysiologically mirrors other experiences.[12,15,21] Another limitation of this study is the nonuniformity of anesthesia applied to the two groups. All patients undergoing STS received general anesthesia, whereas 89% of $C \pm L$ procedures experienced general anesthesia and the remainder were managed with topical and/or local anesthesia. However, the 12 patients managed with topical and/or local anesthesia were additionally managed with interventions in the operating room that addressed posterior lesions that may not have been amenable to treatment in the office.

Although Boyer et al. and Hanks et al. demonstrated the safety and feasibility of performing sclerotherapy in the office setting, this study was not designed to negate the outpatient benefits including less procedural risk and greater cost-savings with this office-based procedure but rather to complement it by performing the same procedure under general anesthesia in the operating room.[15,22] In the office setting, an average of 7 lesions are addressed per session, with patients requiring a mean of 4.3 sessions.[22] In comparison, in this study sclerotherapy performed under general anesthesia allowed all lesions to be injected in one session in a highly controlled setting.

As greater understanding of the pathogenic mechanisms behind recurrent epistaxis in HHT becomes evident, a multifaceted and incremental approach to its management is now being recognized. Patients with mild disease (ESS <4) are treated medically with a focus on various emollients for moisturization and on saline sprays for humidification of the nasal passages to maintain mucosal integrity.[1,6] Surgical treatments still play a central role in the management of patients with moderate and severe disease (ESS ≥4).[6,10] Several of these procedures including septal dermoplasty and the Young's procedure are quite effective but fraught with disadvantages.[11] The advent of antiangiogenic medical therapies, delivered either topically or systemically, has shown promising results in improving blood counts and transfusion needs in HHT.[23] To build upon the results of these data, studies assessing a multimodality combination of medical therapies and STS on impacting hemorrhagic end-points in HHT-related recurrent epistaxis need to be conducted.

CONCLUSION

This study is the first to demonstrate long-term efficacy and safety of STS in the treatment of epistaxis due to HHT. STS was equivalent to $C \pm L$ in maintaining satisfactory disease control, but attained this with significantly fewer procedures and with lower rates of postoperative complications, especially septal perforation, nasal crusting, and foul odor. STS should be considered as the initial choice of surgical intervention in patients with HHT and moderate and severe epistaxis.

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