Complications from office sclerotherapy for epistaxis due to hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu)

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Background: **The aim of this study was to identify and evaluate adverse clinical outcomes following office-based sclerotherapy using sodium tetradecyl sulfate (STS) for epistaxis due to hereditary hemorrhagic telangiectasias (HHT or Osler-Weber-Rendu).**

Methods: **A retrospective chart review of 36 adult patients treated with STS sclerotherapy for severe and/or recurrent epistaxis due to HHT was performed.**

Results: **A total of 153 separate treatment sessions were analyzed. Each patient underwent an average of 4.3 sessions with an average of 7 intralesional injections per session. Bleeding during the procedure was experienced by 8 patients with a maximum reported blood loss of 200 mL in 1 patient, but less than 50 mL in all others. Seven patients reported some postinjection pain, which included nasal, cheek, and eye pain. Nasal congestion, sneezing, and vasovagal responses were each noted to occur 2 times. No complications of postprocedural visual loss, deep venous thrombosis/pulmonary embolus, transient ischemic attack (TIA)/stroke, or anaphylaxis were encountered.**

Conclusion: **Conventional therapies used in the management of HHT-related epistaxis, such as laser coagulation, septodermoplasty, selective arterial embolization, and Young's occlusion each have specific associated complications, including worsened epistaxis, septal perforation, foul odor, nasal crusting, and compromised nasal breathing. STS is a safe office-based treatment option for HHT-mediated epistaxis that is associated with exceedingly few of the aforementioned serious sequelae.** © 2014 ARS-AAOA, LLC.

Key Words:
complications; outcomes; epistaxis; hereditary hemorrhagic telangiectasia; sclerotherapy; sodium tetradecyl sulfate; STS; Osler-Weber-Rendu syndrome

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Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu) is an autosomal dominant multisystem disease affecting the connective tissue and elastic fibers of vasculature throughout the body. Stemming predominantly (90% of cases) from mutations in the transforming growth factor β (TGF-β)/bone morphogenic protein (BMP) angiogenic regulation cascade, including the *Endoglin* (*ENG*) and *ALK1/ACVRL1* loci, HHT showcases hemorrhagic complications through rupture of the characteristically thin-walled, discontinuous vascular architecture, defined by inadequate elastin and smooth muscle fibers. Consequently, these architectural deficits lead to altered hemostasis due to defective vasoconstriction.[1–5] Vascular malformations in HHT manifest via progressive elastin loss and consequent luminal dilatation of postcapillary venules, which is followed by arteriolar and capillary enlargement.[6] This induces an augmentation in microvascular flow, which in turn induces cytoskeletal architecture changes, which eventually lead to the disappearance of intervening capillary beds and give rise to direct arterial-venous blood flow.[3,6] Furthermore, during this process, affected vessels also become longer and more tortuous, commonly meandering toward the nearest mucosal or cutaneous surface where they are at increased exposure to the external environment.[6] The resultant ultrastructural findings are tortuous and dilated superficial vessels (ie, telangiectasias) in the nasal, buccal, and gastrointestinal mucosa, as well as in the superficial skin vessels,

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and arteriovenous malformations in larger vessels in the liver, lungs, and brain.[1,3]

As the primary presenting manifestation of HHT, epistaxis represents an unpredictable, potentially life-consuming complication that is nearly ubiquitous in these patients, affecting approximately 90% of the 1:5000 afflicted individuals before the age of 21 years.[1,7] Typically, epistaxis is a daily nuisance in these patients and arises as a consequence of irritation of the fragile vessels within the nasal mucosa by minor trauma or through crusting from the drying effect of air conduction through the nasal cavity, which results in vascular damage and rupture.[2,3,8] Moreover, incidence, symptom severity, and the degree of systemic involvement of HHT vascular lesions typically increase with age, and severity may range from minor periodic bleeding to severe potentially life-threatening hemorrhage or arteriovenous shunting.[1–4,9,10] Although exsanguination and other life-threatening events in HHT from epistaxis are extremely rare, epistaxis can impose drastically on the quality of life of HHT patients.[1–3] The end result of these manifestations is that HHT patients may be transfusion-dependent, resigned to frequent epistaxis-related hospitalizations, faced with limited social flexibility and reduced occupational productivity, and inflicted with significant psychological sequelae (including anxiety, depression, and social isolation).[1,11]

Depending on the severity and frequency of symptoms, several treatments options for HHT-mediated epistaxis have been reported. In cases of mild recurrent epistaxis, bleeding is often managed conservatively with packing and pressure and may be prevented or lessened in frequency with diligent nasal passage moisturization. However, further demonstrating the troublesome nature of HHT vascular lesions, even conservative therapies like nasal packing may perpetuate a cycle of worsening bleeds by damaging adjacent telangiectasias. Also, packing can alternatively cause necrosis of the nasal cartilage, infections, aspiration, hypoxia, and sepsis.[8,12] Moreover, for recurrent or severe epistaxis, referral to an otolaryngologist is often necessary, and treatment with more invasive modalities may be indicated. Arguably the most troubling aspect of contemporary HHT therapies is that despite the inherent risks and potential long-term sequelae, most therapies exert merely temporizing therapeutic effects rather than serving as cures.[8]

Laser coagulation is a commonly used therapy for telangiectasias in HHT that allows specific targeting of vascular lesions in the nasal mucosa with relatively little collateral tissue damage, and it can be used as successful single-modality treatment for some patients.[11] However, shortcomings of laser coagulation include acute risk of bleeding and the potential need for transfusion, packing, or electrocautery, which can potentially negate the tissue sparing advantages afforded by laser treatment. Furthermore, because the recurrent nature of HHT epistaxis often requires frequent therapeutic interventions and revisions to control symptoms, laser coagulation may put HHT patients at risk of septal perforation if electrocautery or packing is repeatedly used to control acute bleeding, especially if lesions are treated bilaterally. Not only does septal perforation increase the incidence of foul smell and nasal crusting, accumulated tissue damage overlying the fragile telangiectasias from repeated procedures can actually worsen bleeding. Still, repeated laser procedures often do not adequately control bleeding in the long-term, and ultimately septodermoplasty is frequently necessary.[2]

Septodermoplasty is an operative procedure that has the aim of taking the native friable respiratory mucosa of the nasal passages and replacing it with more durable and resilient keratinized squamous epithelium in the form of split-thickness skin grafts.[13] This procedure is frequently associated with drawbacks such as nasal crusting and foul odor. Additional potential complications include decreased sense of smell, an increased risk of sinus infection, reduced ability to breathe nasally, and risk for development of atrophic rhinitis.[8,13] Furthermore, problems can arise with the grafts themselves in the form of inadequate graft coverage or regrowth of telangiectasias through the grafts, which often necessitates repeat or alternate therapies.[2,8]

Endovascular embolization of branches of the external carotid artery using polyvinyl alcohol or embospheres is another option for recalcitrant epistaxis in HHT.[11,12,14,15] The benefit of selective arterial embolization derives from the ability to definitively identify and treat the source of bleeding via microcatheters and contrast-aided angiography. Additionally, embolization allows the assurance that targeted lesions are completely embolized intraoperatively and allows detection of "dangerous anastomoses" between the internal and external carotid systems, which may allow passage of embolic material into the cerebral vasculature.[12,15] Although arterial embolization is often successful in eliminating epistaxis in the immediate postoperative setting, results are typically only short-lived.[11,12] Recurrence of bleeding can be seen from recanalization of embolized vessels or novel vascular growth from the ethmoidal arterial branches resupplying pathologic vessels.[12] The need for repeated invasive endovascular procedures poses many risks such as blindness, transient ischemic attack (TIA)/stroke, systemic infection, and other catastrophic vascular outcomes in addition to possible facial nerve paralysis and cutaneous sloughing.[12,15]

Young's occlusion represents perhaps the most drastic surgical intervention for epistaxis, which acts to reduce epistaxis by surgically occluding the nasal passage, with the goal of completely eliminating airflow over the nasal epithelium. When complete closure is achieved without dehiscence, complete cessation of bleeding is commonly observed postprocedure. However, it has been long hypothesized and has been recently reported that management of epistaxis in a patient with closed nostril(s) can be exceedingly difficult without reversal of the procedure. In fact, Ting et al.[16] reported a case in which a patient who had

previously undergone Young's procedure with initial successful postoperative symptom reduction. However, she then experienced profuse bleeding into the oropharynx that progressed to bilateral aspiration pneumonia and respiratory compromise.[16]

More recently, molecular angiogenesis mediators have been identified as potential therapeutic targets. First used to treat metastatic cancer and neovascular ophthalmologic diseases, Bevacizumab (Avastin) is a monoclonal anti–vascular endothelial growth factor (VEGF) antibody that blocks the VEGF signaling cascade required to form new blood vessels.[17] Importantly, VEGF has been shown to be elevated in HHT due to deactivating mutations in the *ENG* and *ALK1/ACVRL1* genes in the regulatory TGF-β/BMP pathway.[1–5,14,17–19] Therefore, the resultant loss of tonic VEGF inhibition largely responsible for HHT vascular lesions can be counteracted with the anti-VEGF antibody, which can be given alone as a submucosal injection or nasal spray or as an adjunct to potassium-titanyl-phosphate (KTP) laser therapy.[14,17–19] Although intranasal Bevacizumab injections and sprays have been shown to exert lower systemic effects than the intravenous doses used for chemotherapeutic purposes in metastatic cancer, administration of Bevacizumab or other agents inhibiting angiogenesis and local wound healing onto the fragile nasal mucosa in HHT patients is worrisome and with an undefined side-effect profile.[14,18] The increased risk of septal perforation suggested by Chen et al.[18] as a consequence of Bevacizumab injection over the cartilaginous septum is of particular concern. This risk is compounded by the fact that Bevacizumab is routinely administered in conjunction with laser coagulation, which as previously stated has its own associated risks.[18] In addition, no defined dose, frequency, or preferred administration modality has been established in the literature.[14]

For many patients with HHT who suffer from epistaxis that is recurrent or refractory to conventional therapeutic modalities, intranasal sclerotherapy has been demonstrated as a safe, efficacious, and positively life-altering therapeutic option, with successful symptom reduction in as high as 95% of patients treated.[1] Importantly, it has also been established that, compared to conventional modalities, such as laser coagulation, septodermoplasty, and arterial embolization, intranasal sclerotherapy can be performed with relatively few complications, such as persistent nasal crusting, nasal dryness, or foul odor, and it is also less frequently associated with septal perforation than conventional procedures.[1,2] Furthermore, in contrast to laser cautery and septodermoplasty, it has been previously reported that intranasal sclerotherapy can be safely performed without the need of general anesthesia and can be performed on a routine basis in the office.[1,2]

Specifically, previous studies have reported successful and safe sclerotherapeutic management of epistaxis using the agent polydocanol dating back to 2000 with marked success.[1] Similarly, due to its previously established therapeutic benefit in treating large laryngeal and pharyngeal vascular lesions and various other head-and-neck vascular lesions, expanding the therapeutic application of foamed sodium tetradecyl sulfate (STS) has been explored to include the treatment of epistaxis in HHT. In a small sample of patients, all subjects reported a reduction in epistaxis-related symptoms following the administration of intralesional foamed STS, including reduced severity and frequency of epistaxis as well as less frequent need for nasal packing. Furthermore, patients also reported universal satisfaction with the procedure, and all stated that they would undergo the procedure again if symptoms recurred.[2]

The aim of this study is to identify and enumerate potential complications experienced by patients having undergone STS intranasal sclerotherapy for epistaxis and assess these complications and rates of occurrence. Primary outcomes are types of complications and frequency of complications.

Patients and methods

Institutional Review Board approval was granted at the University of Minnesota for this retrospective study. Clinical outcomes of 36 adult patients with severe, recurrent epistaxis as a manifestation of HHT were analyzed via case series for complications following office-based intralesional STS injection from March 2008 to May 2013. Patients diagnosed with epistaxis due to HHT were identified by review of electronic medical records at the University of Minnesota, and individuals previously granting permission for use of protected health information (PHI) in research at the University of Minnesota were considered for the study. Inclusion criteria required that patients undergo at least 1 iteration of in-office STS sclerotherapy during the study. After identification of 42 patients with HHT-mediated epistaxis, 5 were excluded from the study for not meeting this criterion. In 2 cases, patients were selected as candidates for STS sclerotherapy but did not undergo the procedure, opting for an alternate procedure (KTP laser and V-beam laser). The 3 remaining patients underwent exclusively operating room (OR)-based STS injections, largely as measure to control severe bleeding in the systematic OR environment. An additional patient was excluded due to a sclerotherapy procedure performed at an outside medical center that did not meet the standard treatment protocol followed by the authors for this study, who unfortunately experienced a septal perforation as a consequence. Data collection regarding patients and outcomes, including gender, age, dates, and types of previous procedures, comorbidities, and post-procedural complications, was obtained through review of patient electronic medical records for up to 5 years following each procedure. Data analysis consisted of enumeration of complications, patient demographic data, treatment data, and comorbidities from patients' medical charts. This data was then compiled and manipulated as necessary using Microsoft® Excel (Microsoft, Redmond, WA) and its mathematical functions.

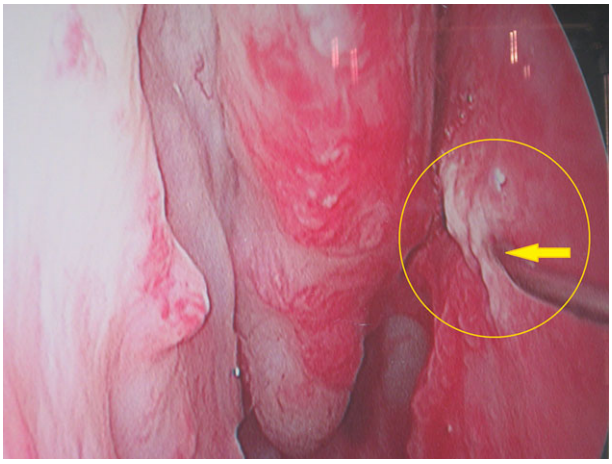

FIGURE 1. Telangiectasia (circle) filling with foamed sclerosant (arrow indicating needle entrance into lesion).

Procedural techniques

Boyer et al.[2] have previously published the treatment protocol used in this series. After application of topical or local anesthetic, telangiectasias are then visualized endoscopically. The interventionist foams the STS with air at a 4:1 ratio and inserts a 25-gauge needle 1 to 2 mm submucosally into the lesion. The solution is then injected at variable quantities with minimal pressure until blanching or extravasation of the sclerosant from the injection site is observed (Fig. 1). If possible, extravasation of STS should be minimized, with the goal of preventing tissue necrosis and cellulitis. The needle is withdrawn after being held in place for several seconds. Each lesion is treated with a discrete injection with a total injected volume not to exceed 3 mL for any given treatment session. Bilateral lesions may be treated cautiously and precisely so as to reduce the risk of septal perforation.[2]

Note: According to the U.S. Food and Drug Administration (FDA), STS is indicated in the treatment of uncomplicated lower extremity varicose veins with competent valves and simple dilation; we used STS for a similar indication but different site.

Results

A total of 42 patients were identified and 36 were selected based upon criteria, consisting of 23 men and 13 women. The average patient age was 58.75 years, with a range of 32 to 91 years. A total of 153 separate treatment sessions were analyzed. Each patient underwent an average of 4.3 sessions with an average of 7 intralesional injections per session. Therapeutic modalities preceding in-office sclerotherapy included sclerotherapy performed in the OR (5 patients), laser cautery (5 patients), septal dermoplasty (8 patients), coblator (2 patients), electrocautery (2 patients), and selective arterial embolization (1 patient). Prior adjunctive measures such as silastic stents, nebulizer moisturization, and septal buttons were used in 2 patients each. Several other modalities were previously documented in one patient each: topical trichloroacetic acid, nasal sling, Epistat, Floseal, Merocel, atenolol, cocaine-packing, Rhino Rocket, oxymetazoline, Bevacizumab, and Afrin-soaked cotton. Additionally, preexisting comorbidities potentially related to HHT-related epistaxis or prior treatments included septal perforation (9 patients), iron deficiency anemia (3 patients), melena (3 patients), hematemesis (1 patient), maggots in nasal cavity (1 patient), synechia (1 patient), and saddle nose deformity (1 patient).

Bleeding during the procedure was experienced by 8 patients with a maximum reported blood loss of 200 mL in 1 patient, but less than 50 mL in all others. The patient who had significant bleeding underwent packing removal in the office, which resulted in hemorrhage prior to attempted sclerotherapy. This patient underwent subsequent repacking and the procedure was then performed in the OR setting. His lesions were sclerosed in the OR on 2 subsequent occasions before he eventually tolerated the procedure very well in the clinic, without the need for packing. Seven patients reported some variation of postinjection pain, which included nasal, cheek, and eye pain. In all cases, postprocedural pain was self-limited, without sequelae, and well-controlled with short-term analgesics. There were no cases of pain persisting longer than several hours and no sensory or other neurological deficits. Nasal dryness occurred in 4 patients, although 1 such complaint may have been confounded by the patient's concurrent use of continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA). Three patients experienced postprocedural vasovagal responses or syncope. Nasal congestion, sneezing, and blood clots in the nasal cavity were each noted to occur 2 times. Postprocedural headache/migraine or foul smell was reported by 1 patient each. There were no incidences of cellulitis or other infection, nausea/vomiting, tissue necrosis, development of new septal perforation, or worsening of an existing perforation. Importantly, no catastrophic postprocedural complications such as visual loss, deep venous thrombosis/pulmonary embolus, TIA/stroke, or anaphylaxis were encountered. A complete summary of patient complications noted following STS infiltration during this study is presented in Table 1.

Discussion

Conventional therapies used in the management of HHT-related epistaxis, such as laser coagulation, septodermoplasty, selective arterial embolization, and Young's occlusion, each have specific associated complications, including worsened epistaxis, septal perforation, foul odor, nasal crusting, and compromised nasal breathing.[8,11–18,20] Moreover, intranasal Bevacizumab is also a promising treatment option but presents the potential for impaired wound healing in the context of an otherwise unproven side-effect profile.[14,18]

STS is a safe, office-based treatment option for HHT-mediated epistaxis that is associated with exceedingly few of the aforementioned serious sequelae. The 2 most

TABLE 1. Complete summary of postprocedural complications noted following intranasal STS sclerotherapy

Complication	Patients with complication (n)
Bleeding during procedure	8
Pain (eye, nasal, cheek)	7
Nasal dryness	4
Vasovagal response/syncope	3
Sneezing	2
Nasal congestion	2
Blood clots	2
Headache/migraine	1
Foul smell	1
Swelling along septum	1
Transient cutaneous pallor	1
Oozing	1
Blood-tinged mucous	1
Noisy nasal breathing	1
Coughing (triggered by topical anesthetic in throat)	1

STS = sodium tetradecyl sulfate.

common side effects of sclerotherapy in the head and neck, as reported in the literature, are tissue necrosis and cellulitis around the site of injection.[2,21] Neither complication was encountered in this study. Rare but more serious complications from STS injections have also been reported, including anaphylaxis and pulmonary embolus, stemming from its use as a sclerotherapeutic agent for varicose veins in the extremities. However, the use of foamed intralesional STS effectively reduces the dosage required to sclerose affected vessels, which both lessens the amount of potential intravascular embolic material and the antigenic load available to the immune system. In comparison to the maximum recommended STS dose of 10 mL per treatment session for varicose veins, neither this study nor the pilot study from which it was derived employed more than 3 mL total per session. Furthermore, visual disturbance is another severe intravascular complication of head and neck injections seen with a vast array of substances, and it has been specifically noted following intranasal sclerotherapy for HHT, with fibrin glue used as the sclerosant. Iatrogenic occlusion of the central retinal artery or ophthalmic artery arises from retrograde embolization of injected material through the ethmoidal arteries or through collateral external-to-internal carotid circulatory connections.[22] A precaution against ocular vascular embolization during intranasal injection includes low-volume intralesional sclerosant placed under the precision of endoscopic lesional visualization and injected at less than diastolic pressure.[2] In a large case series, Morais et al.[1] reported 1 occurrence of septal perforation following intranasal polydocanol injection, but this complication likely could have been prevented with avoidance of simultaneous bilateral septal injection.[1] Other complications of STS reported in the literature that were not seen in this study are as follows: skin ulceration; scarring; and peripheral cranial nerve VII, X, or XII palsies (seen with concurrent alcohol infiltration).[23] Odeyinde et al.[23] have published an excellent summary of techniques to avoid complications in STS sclerotherapy for lymphovenous malformations, many of which are also applicable for intranasal use in HHT. Particularly relevant steps to avoid complications in intranasal injections include the use of a familiar agent (ie, STS), frequent small volume, injections applied under low pressure, and foaming the sclerosant with air.[23] Importantly, the 2 most common side effects of STS injections, tissue necrosis and cellulitis, can be avoided through careful avoidance of extravasation of the sclerosant.[2,21] For treatment of superficial lesions it is advantageous to use a small, long needle inserted with a long subcutaneous trajectory into the lesion while simultaneously lifting the skin. After infiltration, the needle is then gently withdrawn, allowing autologous blood to coagulate and close the needle tract, thereby preventing extravasation of the STS.[23]

Additional inferred benefits of in-office STS sclerotherapy include the cost savings, convenience, and tolerability of performing the procedure in the office. Patients are spared the risk of general anesthetic in most cases. Finally, intralesional STS sclerotherapy can be a transformative procedure for many patients with HHT, previously demonstrated to significantly improve quality of life.[2]

Future studies comparing STS sclerotherapy to standard treatments are currently underway. Additional investigation into the use of STS sclerotherapy *in conjunction with other* treatments, such as topical procoagulants or antiangiogenesis factors, would also be informative. Continual refinement of the technique may also be necessary to improve treatment outcomes and lower the risks of the procedure. Specifically, methods to improve visualization of telangiectasias, refinements of injection techniques, and exploration of other potential sclerosants could be considered. Furthermore, despite the numerous advantages illustrated in this discussion, sclerotherapy, as is commonly true with current nonsurgical treatment modalities in HHT, often must be repeated to gain symptomatic control and to temporize recurrent symptoms. Therefore, methods to reduce the need for repeated procedures would also improve the overall acceptance of this therapy for treatment of intranasal telangiectasias and bleeding.

It should be noted that this study has inherent limitations due to its retrospective nature, including its reliance on prior clinical documentation lacking the possibility for formal systematic assessment for every complication in each patient, unless specifically mentioned by the provider. Therefore, future studies should also include a prospective analysis of the potential complications of STS sclerotherapy. An additional potential weakness of the study was

that patients were not rigorously excluded from the study if they had recently undergone other therapies or adjunctive treatments for epistaxis in addition to STS sclerotherapy. The effects of the supplemental procedures may have potentiated the therapeutic effects of the STS procedure and, thereby, may have affected this study's results regarding both short-term and long-term complications.

Conclusion

Intralesional sclerotherapy with STS for epistaxis related to HHT can be performed in the office setting with a paucity of significant patient morbidity. This therapy should be considered in the armamentarium of treatment for patients with HHT who suffer with recurrent epistaxis.

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