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Antiestrogen Therapy for Hereditary Hemorrhagic Telangiectasia: A Double-Blind Placebo-Controlled Clinical Trial

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Objectives/Hypothesis: Hereditary hemorrhagic telangiectasia (HHT) is associated with recurrent epistaxis in 90% of cases. Good response to hormone treatment has been documented, although its use remains controversial. The aim of this study was to examine the efficacy of an antiestrogenic agent, Tamoxifen, in the treatment of HHT-associated epistaxis.

Methods: Twenty-five patients (11 men, 14 women; mean age 51 years) with a diagnosis of epistaxis due to HHT were randomly assigned to receive treatment with oral tamoxifen 20 mg/d or placebo for 6 months. Follow-up consisted of physical examination and once-monthly blood tests.

Results: The groups were similar in age and sex distribution. Of the 21 participants who completed the trial, alleviation of the epistaxis was noted in 9 of 10 tamoxifen-treated patients and 3 of 11 placebo-treated patients (including 2 with only temporary improvement). The difference between the groups at the trial end point was significant for both frequency ($P = .01$) and severity ($P = .049$) of the disease. Hemoglobin concentration rose in 4 tamoxifen-treated patients and decreased in 5 controls.

Conclusions: Tamoxifen appears to be an effective agent for the treatment of epistaxis due to HHT.

Key Words: Tamoxifen, hereditary hemorrhagic telangiectasia, epistaxis.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease,[1,2] is an autosomal-dominant blood vessel disorder that leads to localized angiodysplasia.[3] Ultrastructural analyses have failed to demonstrate a unique pathologic abnormality. The literature contains various suggestions for the etiology of HHT, namely, endothelial cell degeneration, defects in endothelial junctions, lack of elastic fibers with incomplete smooth muscle coating of the vessels, and weak connective tissue surrounding the vessels.[4]

Because of the fragility of the blood vessels in HHT, even mild trauma can instigate bleeding.[4] Recurrent epistaxis is the most common presenting symptom, occurring in more than 90% of patients.[5] Telangiectasia may also be present (64% of patients) in the skin, conjunctivae, oral cavity, pharynx, and gastrointestinal tract. Less common but more serious manifestations include arteriovenous malformations (48%), intracranial (9%) or pulmonary (15%) aneurysms, progressive liver disease (atypical cirrhosis), and high-output cardiac failure.[6,7]

The treatment of epistaxis in HHT can be difficult because simple routine measures such as cautery and packing may actually exacerbate the bleeding and rarely lead to a durable response.[5] In more than 50% of cases, the disease progresses with time,[8] prompting aggressive treatment measures such as laser photocoagulation, septodermoplasty, intranasal forehead flaps, complete nostril closure, embolization of the nasal vasculature, arterial ligation, and brachytherapy.[5,6,9,10]

There is no recognized medical therapy for HHT-related epistaxis, although some studies reported a positive response to antifibrinolytic agents such as systemic aminocaproic acid and intranasal tranexamic acid.[11,12] Others noted favorable results for estrogen,[13–15] estrogen plus testosterone,[13] estrogen plus progesterone,[16,17] progesterone,[18] and intranasal topical estrogen.[19] However, there is still no consensus regarding hormonal treatment. One double-blind controlled clinical trial showed no significant reduction in the frequency or intensity of epistaxis in patients treated with systemic estrogen.[20]

Recent case reports have described two patients with HHT, one with chronic gastrointestinal tract bleeding[21] and one with severe epistaxis,[22] who responded promptly to treatment with tamoxifen, an antiestrogenic drug usually administered to patients with breast cancer. The aim of the present study was to investigate the

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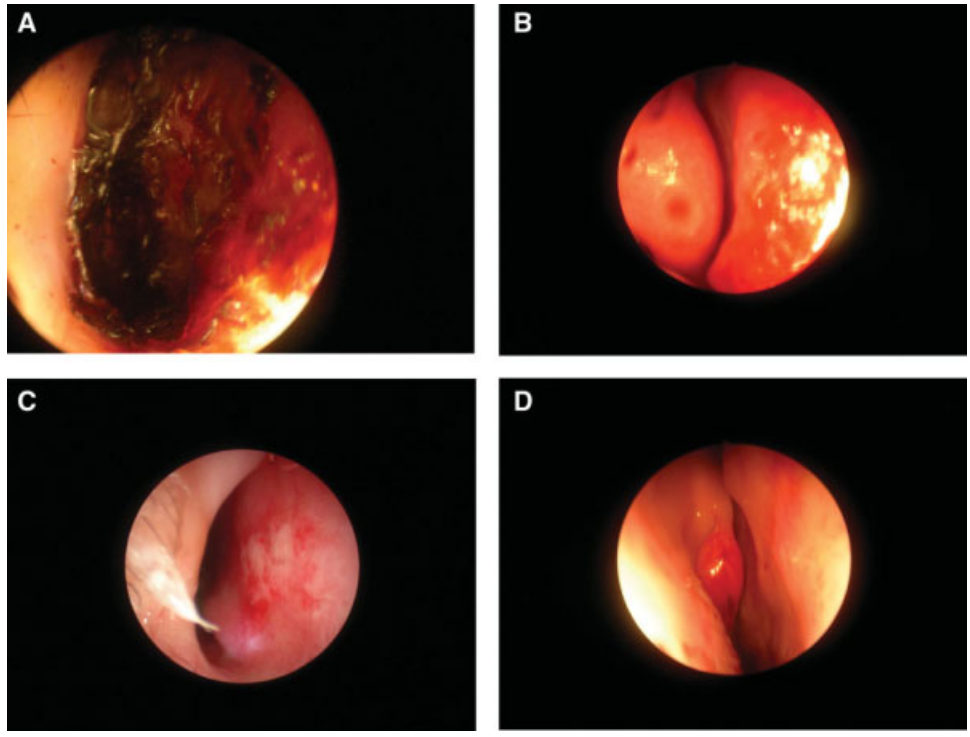

Fig. 1. Severity of nasal condition by endoscopy. (A) Very severe. Nasal mucosa is full of blood clots. (B) Severe. More than 50% of the nasal mucosa is covered by telangiectactic lesions. (C) Moderate. Less than 50% of the nasal mucosa is covered by telangiectactic lesions. (D) Mild. Small amount of blood clots.

effect of tamoxifen in the treatment of severe epistaxis using a double-blind, placebo-controlled design.

MATERIALS AND METHODS

Twenty-five patients with HHT-related epistaxis who attended our center from February 2005 to January 2006 were randomly assigned to 6 months of treatment with either Tab. tamoxifen 20 mg once daily or placebo. The pharmacy of the hospital arranged a list of the treatment-placebo versus tamoxifen before the beginning of the trial. Each patient received a protocol number at the beginning of the trial and received treatment according to his protocol number. The group included 11 men and 14 women aged 28 to 75 years (mean 51). HHT was diagnosed according to the clinical criteria established by the Scientific Advisory Board of the HHT International Foundation.[23] The presence of three of the four criteria, namely spontaneous recurrent epistaxis, cutaneous telangiectases, visceral involvement, and family history, was considered diagnostic.

A detailed medical history was taken at presentation. On physical examination, all patients had grade 2 or 3 epistaxis, according to the standardized protocol of Bergler et al.[24] The patients were examined by an otolaryngologist before and once monthly during the trial to assess the nasal condition and blood clots in the airway, nasal and oral cavity, and skin. The severity of the nasal telangiectasis was determined by endoscopy and categorized as follows: (4) very severe: nose full of blood clots (Fig. 1A); (3) severe: more than 50% of the nasal mucosa covered by telangiectatic lesions (Fig. 1B); (2) moderate: less than 50% of the nasal mucosa covered by telangiectactic lesions (Fig. 1C); (1) mild: only a few lesions (Fig. 1D).

Blood was collected for measurement of blood count, clotting time, and liver function at onset of the trial and once monthly during treatment. Patients were requested to complete a daily chart describing the course of their epistaxis, and female patients were referred for gynecologic follow-up, including ultrasound, once a month.

The study was approved by the Ethics Committee of Rabin Medical Center. All patients signed a consent form.

Statistical Analysis

Continuous parameters were recorded as means ± standard deviations. Pearson correlation coefficient (r) and the significance for it (P) were calculated between the variables.

Student t test was used to analyze differences in continuous variables between the two treatment groups (tamoxifen and placebo), and χ^2 test or Fisher exact test was used, as appropriate, to analyze differences in categorical data. Values less than or equal to .05 were considered statistically significant.

RESULTS

There was no difference between the two groups of patients in age and sex distribution, or in frequency and duration of epistaxis, hemoglobin level prior to treatment, or initial disease severity (Table I).

Twenty-one of the 25 patients completed the 6-month trial. Reasons for attrition included residence far from the center in one patient of the tamoxifen group (who showed improvement), severe pelvic and knee pain in one patient in the placebo group, and failure to improve after 4 months in another two patients in the placebo group.

Of the 10 remaining patients in the tamoxifen group, nine showed improvement in both the frequency and severity of epistaxis, by both self-report and endoscopic examination (Table I), starting in the first month of treatment in six patients and after 2 months in three patients. One patient failed to show improvement. In the placebo group, the epistaxis improved during the first 3 months of treatment in two patients, but reverted by the end of the trial. One patient showed improvement during the fifth and sixth months of treatment.

TABLE I.
Severity of Nasal Condition Before Treatment and at the End of Trial.

Severity of condition	Tamoxifen (n=10)		Placebo (n=11)	
	Before trial	End of trial	Before trial	End of trial
Mucosal telangiectasis				
Very severe	3		2	4
Severe	3	5	3	3
Moderate	4	2	5	3
Mild		1	1	1
No telangiectasis		2		
Need for blood transfusion				
Frequently*	2		1	
Occasionally*	1		3	2

*Frequently – more than 6 times yearly. Occasionally – less than 6 times yearly.

By the end of treatment, there was no change in the epistaxis in the placebo group. There was a significant difference between the groups at the 6-month follow-up in both frequency ($P = .01$) and severity ($P = .049$) of epistaxis. Nine of 10 patients in the tamoxifen group reported significant improvement in quality of life (QOL) versus only one of 11 in the placebo group.

As we did not anticipate QOL to be an important parameter, we did not include a QOL questionnaire in the research. However, after we realized the importance of this parameter, we asked all the patients at each visit about QOL. Statistical analysis with Fisher exact test showed that QOL improved significantly ($P = .0001$).

Hemoglobin concentration increased in four patients in the tamoxifen group and in three in the placebo group. A drop in hemoglobin concentration was noted in five patients in the placebo group. The difference between the groups in hemoglobin concentration was not significant. In the tamoxifen group, blood transfusions had been required on a regular basis in two patients—sometimes up to 8 units per month—and occasionally in one. In the placebo group, blood transfusions had been required on a frequent basis in one patient and occasionally in three. After onset of the trial, blood transfusions were required by two patients in the placebo group and in none of the study group.

All patients had telangiectactic lesions at onset of the trial: 17 in the mouth and on the tongue (Fig. 2) and 16 on the face and ears. In the tamoxifen group, the lesions decreased in size in four patients, and some of them disappeared in three patients. The placebo group showed no change in the facial and oral lesions.

One patient each in the study and placebo group had nasal septal perforations due to previous coagulation/surgery, and 15 patients, seven in the tamoxifen group and eight in the placebo group, had a blocked nose due to mucosal swelling, large telangiectasis scar tissue, and blood clots. After treatment, five patients in the study group showed considerable improvement in the nasal airway blockage and a decrease in the number and size of the telangiectactic lesions. One patient in the placebo group also showed resolution of a blocked nasal passage.

The only side effect of treatment was an ovarian cyst in one patient, which later disappeared spontaneously. Seven of the nine patients in the tamoxifen group who responded to treatment reported that their quality of life had improved dramatically and they were no longer afraid to leave their home.

Indeed, one patient flew to another country for the first time in 20 years. After tamoxifen treatment was stopped, the patients' conditions deteriorated within 2 to 6 weeks.

DISCUSSION

The present study describes the use of a promising novel antihormonal treatment for epistaxis in patients with HHT.

HHT is an autosomal-dominant vascular dysplasia caused by mutations in the endoglin (ENG) gene (HHT1) or the ACVRL1/ALK1 gene (HHT2). Recently, several other genes were found to play a role in HHT (MADH4/JPHT/BMPRH/PPH; HHT3).[25–27] However, a positive finding on DNA sequencing has not yet been included

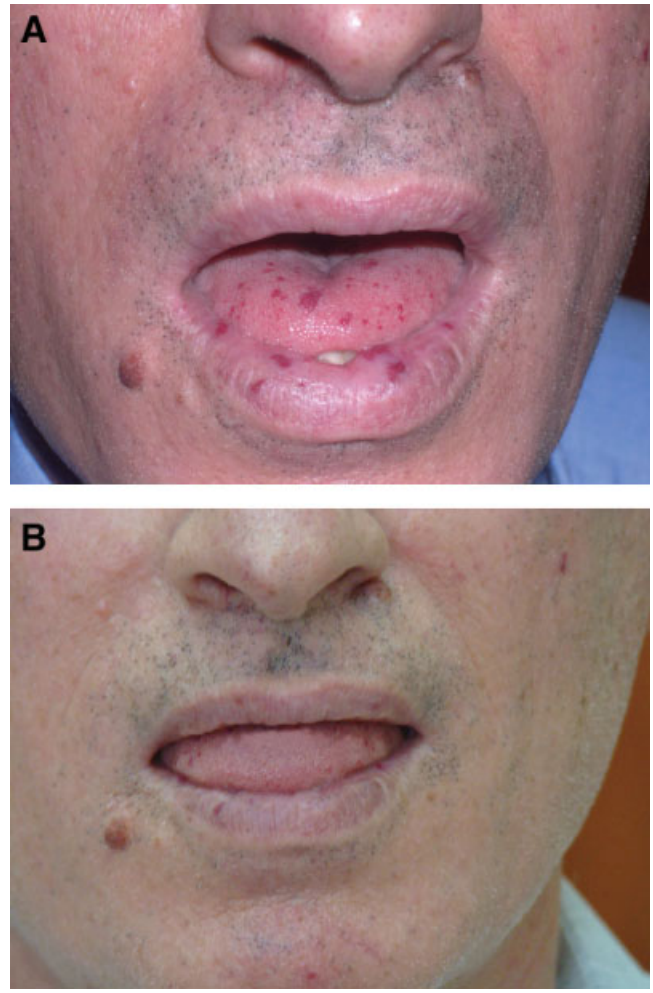

Fig. 2. Telangiectactic lesions on the lower lip and tongue. (A) Before treatment. (B) Six months after treatment.

among the accepted diagnostic criteria.[26] In our series, all patients had at least three of the four established criteria for diagnosis,[23] and all had grade 2 or 3 epistaxis.[24]

Clinically, HHT is a chronic systemic disease that severely affects the quality of patients' lives. Owing to the recurrent epistaxis, patients are afraid to leave home or to travel.[22] Some have severe anemia and require blood transfusions.[5,8] HHT may also present in other body areas, causing gastrointestinal bleeding, aneurysms, hepatic bleeding with progressive liver disease (atypical cirrhosis), and high-output cardiac failure.[6,7] To the best of our knowledge, there is currently no effective treatment. The use of nasal packing, coagulation, and surgery for the nasal epistaxis may cause scarring and narrowing of already blocked airways. In our series, 15 patients had blocked nasal airways and two had nasal septal perforations.

At present, estrogen is the most popular pharmacologic treatment for HHT-associated telangiectasis, with favorable results reported in several studies.[13–17,19] The rationale for its use is based on estrogen's ability to provoke squamous epithelial metaplasia, which protects superficial telangiectacic vessels from breaking down and bleeding.[23] In addition, studies have reported the detection of two estrogen receptors (alpha and beta) in patients with HHT.[23] However, in the only double-blind controlled clinical trial conducted to date, estrogen showed no significant benefit in reducing the frequency and intensity of epistaxis.[20]

Our study was based on the assumption that when estrogen binds to its receptors in patients with HHT, it induces proliferation of the blood vessels and, thereby, the creation of telangiectactic lesions. Therefore, we sought to determine if an antiestrogen agent that blocks the receptors would reverse this process. According to our results, treatment with tamoxifen was effective in most cases in reducing the frequency and amount of epistaxis compared with placebo, with almost no side effects. Endoscopic examination revealed an improvement in the nasal condition throughout treatment. Patients also described significant improvement in QOL.

The present study is limited by the small sample size and short duration of treatment. Tamoxifen appears to be a promising agent for the treatment of epistaxis in patients with HHT, and larger, longer-term trials are warranted to corroborate our findings. In addition, studies to increase our understanding of the genetics of HHT could lead to predictive methods associating genotype with response to tamoxifen.

CONCLUSIONS

Tamoxifen appears to be an effective agent for the treatment of epistaxis due to HHT. None of the patients treated with tamoxifen required blood transfusion during the treatment period. Most patients reported improvement of QOL during treatment. The only side effect of the treatment was an ovarian cyst in one patient.

We believe tamoxifen is a useful treatment modality for patients with HHT and severe epistaxis.

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