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Managing epistaxis in hereditary haemorrhagic telangiectasia: a comprehensive narrative review of therapeutic horizons

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Main Article

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Abstract

Background. Hereditary haemorrhagic telangiectasia is an autosomal dominant vascular disorder characterised by mucocutaneous telangiectasia, leading to recurrent epistaxis in nearly all affected individuals. Treatment strategies are broadly categorised into conservative, medical and surgical approaches. This study aimed to provide a concise summary of the existing literature on epistaxis associated with hereditary haemorrhagic telangiectasia.

Methods. The Medline/PubMed database was searched for relevant articles using the keywords 'hereditary haemorrhagic telangiectasia', 'Osler-Weber-Rendu' and 'epistaxis'.

Results. Out of 93 reviewed articles, 59 contained pertinent information. Interventions were categorised into self-delivered therapy, intravenous treatment, in-office procedures and surgical intervention.

Conclusion. A stepwise approach to managing epistaxis in patients with HHT involves a gradual escalation of treatments, starting with conservative measures and progressing to more invasive interventions as necessary. Topical oils can be efficient and intranasal bevacizumab injection shows promise, but more data are needed. Surgical options range from bipolar cautery and laser therapy to complete closure of the nasal cavity. Proper patient selection remains crucial.

Introduction

Hereditary haemorrhagic telangiectasis(HHT) is an autosomal dominant vascular disorder with incomplete penetrance that is characterised by mucocutaneous telangiectasis. Involvement of the nasal lining leads to recurrent treatment-resistant nose bleeds. Additional diagnostic criteria include disease in a first-degree relative and visceral arterio-venous malformations.[1] The Curaçao criteria are summarised in Table 1.[2] When the clinical picture is incomplete, identification of a heterozygous pathogenic variant in *ACVRL1, ENG, GDF2*, and *SMAD4* genes is diagnostic.[3]

The highest prevalence of hereditary haemorrhagic telangiectasis, 1 in 1331, is seen in the Afro-Caribbean residents of the Netherlands Antilles.[4] The prevalence in North America, Europe and Japan ranges between 1 in 5000 and 1 in 10 000.[1,5–7]

Almost all patients will suffer from epistaxis during their lifespan and more than half will do so before the age of 20 years.[4,8,9] The recurrent nose bleeds will lead eventually to anaemia, resulting in a significant increase in medical costs and a decrease in quality of life (QoL).[3,10] A strong correlation was found between age and poor QoL, highlighting the increasing burden of the disease over time.[10]

Since its description by Osler[11], Weber[12] and Rendu[13] more than 100 years ago, myriad hereditary haemorrhagic telangiectasia-related epistaxis management strategies have been reported. In the acute setting, the Airway Breathing Circulation (ABC) approach should be implemented and packing with resorbable material is preferred.[3] This article aims to review and summarise the recent literature.

Methods

We thoroughly searched Medline/PubMed to identify relevant articles published in the last 15 years. Keywords included 'hereditary haemorrhagic telangiectasia', 'Osler-Weber-Rendu' and 'epistaxis'. Abstracts were reviewed and those focusing on epistaxis management were selected.

Overall, 59 articles were examined in depth by 2 reviewers independently. The pertinent findings are summarised in this article.

Table 1. The Curaçao Diagnostic Criteria for hereditary haemorrhagic telangiectasia

Criteria	Description
Epistaxis	spontaneous, recurrent nose bleeds
Telangiectasis	Multiple, at characteristic sites
	Lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal telangiectasia (with or without bleeding)
	Pulmonary arterio-venous malformation
	Hepatic arterio-venous malformation
	Cerebral arterio-venous malformation
	Spinal arterio-venous malformation
Family history	A first-degree relative with hereditary haemorrhagic telangiectasia according to these criteria
Diagnosis	
Definite	Three criteria are present
Possible or suspected	Two criteria are present
Unlikely	If fewer than two criteria are present

Self-delivered therapy

Droege *et al*. published a survey about self-packing.[14] Out of the 588 responders, almost two-thirds self-performed nasal packing, 52 per cent of them using medical packing and the rest using only tissues. The highest score on the Glasgow Benefit Inventory was achieved when using a pneumatic packing device, despite this being more painful.

Because turbulent airflow is believed to be traumatic to the telangiectasis, reversible nasal occlusion is considered when other therapy fails. Woolford *et al*. reported on three patients with recalcitrant epistaxis that decreased significantly after using a Silastic nasal obturator. While this study did not specify how long the obturator was applied throughout the day, patients commented that they preferred to remove the obturator while eating to restore their sense of smell.[15] In another study, 20 patients undergoing laser therapy at regular intervals performed nasal occlusion with a hypoallergenic tape for 5 hours a day. After 3 months, the epistaxis severity score decreased by 1.16 points and haemoglobin remained stable.[16]

When 20 patients were prescribed sesame and/or rose geranium oil topical compound for a minimal duration of 3 months, the epistaxis severity score decreased by 1.81 ($p < 0.0001$). Although the mechanism of action is not quite clear, the benefit seems to be coming from the combination of nasal hydration and the formation of a durable protective layer.[17]

Bevacizumab spray did not show superiority to placebo in a meta-analysis of three randomised, controlled trials (RCTs).[18]

In an RCT, intranasal tranexamic acid and estriol showed no decrease in epistaxis frequency or duration. All groups, including placebo, improved the epistaxis severity score at weeks 12 and 24.[19] Tranexamic acid stabilises blood clots by inhibiting fibrinolysis. The mechanism of action of estriol is by inducing squamous metaplasia.[19]

Tacrolimus exhibits anti-angiogenic properties by targeting the BMP9/ALK1/ENG/SMAD pathway.[20] In a study, 50 patients were randomised for treatment with 0.1 g intranasally of 0.1 per cent tacrolimus twice a day versus placebo for 6 weeks. No significant difference in epistaxis duration and frequency was found six weeks after cessation of therapy. However, during treatment, this difference was significant. Since the toxicity of topical tacrolimus is not known, the authors did not recommend a longer treatment duration to maintain the observed benefit.[20]

de Jel *et al*. reported their experience with topical fluorouracil, known for its ability to promote the formation of scar tissue.[21] Six patients with haemorrhagic telangiectasia-related epistaxis were treated on the side that bled the most with a 4.5-cm nasal tampon with 1 ml of 50 mg/g fluorouracil and 1 ml of normal saline. The same protocol was repeated once a week for four weeks. After treatment, there was a significant improvement in nasal mucosa score, epistaxis severity score and haemoglobin levels. No significant side effects were reported. The patient described a bad smell and dry sensation in the throat at the end of the treatment. The study did not include a control arm.[21]

Non-selective beta blockers, namely propranolol, are used routinely to treat infantile haemangiomas. The possible mechanisms of action include both vasoconstrictive and antiangiogenic effects by reducing vascular endothelial growth factor-stimulated angiogenesis.[22] In an RCT, twice-daily propranolol nasal gel showed superiority to placebo after eight weeks of treatment. In the treatment group (10 participants), the epistaxis severity score decreased from a mean of 6.50 ± 1.84 to 4.47 ± 1.75 ($p = 0.004$), haemoglobin numbers increased significantly and transfusion requirements decreased. None of these parameters changed significantly in the placebo group (10 participants).

This period was followed by an open-label eight-week study, in which seven participants from the treatment group and eight from the placebo group used propranolol gel twice daily for an additional eight weeks. The beneficial effect was preserved in the previously treated group and the epistaxis severity score improved significantly in the former placebo group (-1.99 ± 1.41, $p = 0.005$). No systemic side effects were observed. The most common side effect was a burning sensation that decreased with continued treatment.[22]

Thermosensitive intranasal timolol (0.1 per cent) gel for 8 weeks did not show definitive superiority to placebo. The epistaxis severity score and QoL improved in both groups. The authors concluded that the use of a thermosensitive gel with or without timolol is appropriate for patients with hereditary haemorrhagic

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telangiectasia.[23] Dupuis-Girod *et al.* used timolol spray and found no significant difference in outcome between the treatment and control groups.[24]

In a randomised, double-blind, placebo-controlled, crossover phase IIIB study involving 22 patients, the effects of 1 g of tranexamic acid administered three times daily were compared with those of a placebo over a period of 6 months. Despite the treatment, haemoglobin levels remained statistically unchanged. However, a significant 54 per cent reduction in epistaxis was observed. It is important to note that the treatment effect was heterogenous and the distribution of epistaxis scores was notably skewed.[25] In a similar study with 118 patients, tranexamic acid led to a 17.3 per cent reduction in the duration of epistaxis, although there was no significant change in the frequency of epistaxis compared with placebo.[26] A 2019 meta-analysis found no statistically significant difference between tranexamic acid and placebo.[18]

Oral oestrogen for three months showed no improvement in haemorrhagic telangiectasia-related epistaxis frequency or duration.[18]

Anti-oestrogen agents are used in hereditary haemorrhagic telangiectasia patients because it is believed that oestrogen, when binding to its receptors, triggers the formation of blood vessels. Blocking this interaction aims to halt or reverse the formation of telangiectasis. In a double-blind placebo-controlled clinical trial aiming to investigate the effectiveness of tamoxifen in treating haemorrhagic telangiectasia-related epistaxis, 25 patients were randomly assigned to receive tamoxifen 20 mg daily or a placebo for 6 months. Based on the grading system suggested by Bergler *et al.*[27] tamoxifen was significantly more effective in reducing the frequency ($p = 0.01$) and severity ($p = 0.049$) of epistaxis compared with the placebo. Additionally, tamoxifen led to a non-significant increase in haemoglobin levels in some patients. One patient in the treatment arm developed an ovarian cyst that resolved spontaneously.[28]

Contis *et al.* reported on their experience with systemic propranolol.[29] The study included a retrospective group of 10 patients already on propranolol for cardiac or neurological reasons and another prospective group of 11 patients. In the former group, the epistaxis severity score significantly decreased from a median of 8.3 (range, 7.98–9.44) to 4.5 (range, 4.31–6.61) ($p = 0.003$) with a median duration of treatment of 16.5 months (range, 12–22.75 months). In the latter group, with a dose of 40 mg twice daily, the median cumulative duration of epistaxis per month was reduced from 2.8 hours (range, 2.28–7.56 hours) to 0.71 hours (range, 0.27–3.76 hours) after 3 months of treatment ($p < 0.0001$). The median number of epistaxis episodes per month decreased from 27 episodes per month (range, 15–56 episodes per month) to 14.5 episodes per month (range, 8–27 episodes per month) ($p < 0.0001$) at 3 months and the median number of days without epistaxis per month increased from 9 days (range, 5–18 days) to 17 days (range, 11.5–23.5 days) after 3 months of treatment ($p = 0.01$). The epistaxis severity score was not reported in the prospective group.[29]

Oral itraconazole, an antifungal drug with inhibiting effects on vascular endothelial growth factor, 200 mg daily for 16 weeks, significantly decreased the epistaxis severity score and the monthly epistaxis frequency. However, haemoglobin levels did not significantly change. Four out of 21 patients prematurely interrupted the study, 3 of them for mild or moderate side effects.[30]

Intravenous treatment

The pathogenic effects of hereditary haemorrhagic telangiectasia are largely driven by vascular endothelial growth factor. Research has shown that normalising vascular endothelial growth factor levels can effectively prevent arterio-venous malformations in mice lacking Acvrl1.[31] Consequently, bevacizumab, a monoclonal antibody that blocks vascular endothelial growth factor signalling, has become a promising therapeutic candidate.[32]

The International HHT Intravenous Bevacizumab Investigative Team study of Bleeding (InHIBIT-Bleed) evaluated the efficacy of intravenous bevacizumab on haemorrhagic telangiectasia-related epistaxis and gastrointestinal (GI) bleeding. In total, 143 patients were included in the epistaxis analysis. The mean epistaxis severity score decreased by 3.37 points after treatment and clinically meaningful reduction in epistaxis, defined as an epistaxis severity score reduction of 0.71 or more post-treatment, was achieved in 92 per cent of patients. The reduction was noticeable after three months of treatment. Mean haemoglobin increased and the need for transfusion decreased after treatment. However, this is the effect of a combined reduction in epistaxis and GI bleeding. Overall, 12 patients (5 per cent) discontinued bevacizumab because of adverse events.[33] The adverse effects of bevacizumab may include hypertension, proteinuria, venous thromboembolism, intestinal perforation and poor wound healing. Paradoxically, bevacizumab is associated with a significant risk of epistaxis in non-hereditary haemorrhagic telangiectasia patients.[32]

A cost-effectiveness analysis of systemic bevacizumab therapy in hereditary haemorrhagic telangiectasia found that, regardless of willingness to pay, the addition of long-term intravenous bevacizumab to the current standard of care improves the quality-adjusted life expectancy of patients with hereditary haemorrhagic telangiectasia and appears to be a cost-saving intervention compared with the current standard of care alone.[34]

The Dutch hereditary haemorrhagic telangiectasia expertise centre evaluated the efficacy of tacrolimus on haemorrhagic telangiectasia-related epistaxis. In this study, 25 patients received 1 mg of tacrolimus a day for 20 weeks. The daily dose was adjusted for a trough level between 2 and 3 μg/l. Two patients did not continue the study due to serious side effects and two due to non-serious side effects. Epistaxis severity score, duration and severity of epistaxis decreased significantly, especially in the group with no GI bleeding. Haemoglobin levels did not change significantly in patients with epistaxis or GI bleeding alone.[35]

Pazopanib, a highly selective vascular endothelial growth factor receptor inhibitor, dramatically improved epistaxis in a patient with haemorrhagic telangiectasia-related epistaxis not responding to multiple courses of intravenous bevacizumab.[36]

In-office procedures

Multiple regimens of submucosal bevacizumab injections have been suggested, most ranging between 25 and 100 mg. In an RCT on 15 patients (9 in the treatment arm, 6 in the placebo arm) receiving a single injection of 100 mg of submucosal bevacizumab, there was a trend at 3 months towards better visual analogue scale (VAS) scores, better epistaxis severity score and a decrease in daily minutes of epistaxis. None of these changes reached statistical significance when compared with placebo. The study was underpowered because the required number of participants, in theory, cannot be reached in practice. Side effects included high blood pressure (one event), rhinitis (one event), three days of whole-body tingling (one event) and nasal tip itching (one event).[37]

Another recent RCT compared bevacizumab to saline injections in patients undergoing surgical cauterisation for haemorrhagic telangiectasia-related epistaxis. The minimal clinically important difference of the epistaxis severity score was set at 0.71.

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Thirty-seven patients were included and all received a single injection. The additive benefit of bevacizumab over saline exceeded the minimal clinically important difference at one, two and four months, but the difference was not statistically significant.[38]

Karnezis and Davidson published efficacy data on 10 patients receiving 100 mg of bevacizumab submucosally and 5 patients receiving both submucosal and intranasal bevacizumab.[39] Twelve patients were treated concurrently with a potassium titanyl phosphate (KTP) laser. After a mean period of follow up of 4.1 months (range,1.15–19.15 months), the epistaxis severity score decreased from 7.0 (standard deviation (SD) = 2.1) to 2.9 (SD = 1.7) ($p < 0.0001$). The same group reported safety data showing that combined treatment of the cartilaginous septum with bevacizumab injections and laser therapy resulted in high rates of septal perforation.[40]

A recent meta-analysis of 7 studies (3 nasal spray, 3 intranasal injection only, 1 intranasal injection and laser) showed an improvement in the epistaxis severity score (Weighted Mean Deviation = −0.22, 95 per cent confidence interval (−0.38, −0.05), $p = 0.01$]. There was no significant effect on epistaxis duration and frequency.[41]

In a recent systematic review of 196 patients, sclerotherapy led to an improvement in haemorrhagic telangiectasia-related epistaxis in all of the 7 included studies. Three studies reported outcomes on an epistaxis severity score scale, three used the Bergler-Sadick scale and one study used subjective surveys. This heterogeneity in reporting outcomes precluded formal meta-analysis.[42]

In a retrospective chart review of 36 adults and 153 treatment sessions, no post-procedural visual loss, deep venous thrombosis and/or pulmonary embolus, transient ischaemic attack and/or stroke, or anaphylaxis were encountered. Reported complications included per-procedure bleeding, mostly mild, and some post-injection nasal, cheek and eye pain. Less frequent complications include nasal congestion, sneezing and vasovagal responses.[43]

Surgical intervention

Ghaheri *et al.* described their experience with bipolar electrocautery.[44] Over 8 years, 42 bipolar procedures were performed over 18 patients. The laser was used as an adjunct in 22 procedures. Nine patients required more than one intervention. The average time interval to follow-up surgery was 7.5 months. No septal perforation or synechia were noted.[44]

In a systematic review in 2020 with a total of 362 patients, argon and neodymium-doped yttrium aluminium garnet (YAG) laser therapy was around 90 per cent effective in reducing haemorrhagic telangiectasia-related epistaxis frequency and severity. Neodymium-doped YAG laser therapy seems to be more efficient for severe epistaxis than argon laser therapy. Diode laser therapy was significantly inferior, with a 71.1 per cent success rate.[45] No post-operative complications were described with these three laser types.[46–48]

In an RCT, coblation and a KTP laser were found to be equally effective in controlling haemorrhagic telangiectasia-related epistaxis. Nasal obstruction VAS scores were significantly lower in the coblation group.[49] Rotenberg *et al.* had equally good results in 37 patients they treated with coblation over 3 years.[50] Three of their patients suffered from a septal perforation. They all had multiple septal cauterisations in the past. In a case series of five patients, haemostasis was found to be difficult to achieve with coblation in a patient with severe disease.[51]

For severe refractory disease, septodermoplasty is an option. It has the advantage of replacing a large area of diseased mucosa. Telangiectasias can re-grow on the skin graft.[9] However, the need for laser therapy after septodermoplasty decreased significantly, from 1.83 ± 1.99 to 0.78 ± 0.85 laser treatments in a study spanning over 60 months.[52] To balance the risks of septal perforation, increased crusting, decreased cessation of airflow, loss of olfaction and the precipitation of atrophic rhinitis, Harvey *et al.* beleive that a septodermoplasty is suitable for patients with less than six months of epistaxis control after three laser treatments.[52]

Super-selective embolisation of branches of the external carotid artery achieved immediate haemostasis in 12 of 14 patients with refractory haemorrhagic telangiectasia-related epistaxis. In addition, 11 of 12 patients available for the 24-month follow up reported a reduction in frequency and severity of epistaxis.[53] Compared with idiopathic epistaxis, haemorrhagic telangiectasia-related epistaxis requires multiple endovascular and surgical treatments over time.[54]

In a study by Dabiri *et al.* where bilateral endonasal cauterisation of branches of the sphenopalatine, anterior and posterior ethmoids was performed, the epistaxis severity score decreased by more than 50 per cent in 4 of 5 participants at 9 months.[55] The one patient that did not fall into this category had the posterior ethmoid cauterised only on one side because of a cerebrospinal fluid (CSF) leak. The contralateral artery was shown to be involved in the epistaxis at pre-operative angiography. One of 5 patients maintained a more than 50 per cent reduction of epistaxis severity score 12 months after the surgery. All patients had embolisation of the Sphenopalatine artery (SPA) before the surgical intervention.

In another study, 43 patients with severe intractable haemorrhagic telangiectasia-related epistaxis underwent surgical nasal closure (38 bilateral, 5 unilateral (patient's choice)).[56] Seven patients were lost to follow up. Thirty of 36 patients experienced a complete cessation of epistaxis and 5 patients experienced minor posterior epistaxis. Post-operative haemoglobin data was available for 16 patients. There was an average increase of 4.68 g/dl. Furthermore, all patients reported feeling better after the surgery and that they would rather have the side effects of Young's procedure (xerostomia, anosmia or decreased taste) than epistaxis.[56]

Another article examined the outcome of surgical nasal closure in 100 patients (87 bilateral, 13 unilateral). Ten patients developed small pinholes that led to bleeding. These were managed successfully with primary closure and nasolabial flap (two patients). Two cases were less successful, one due to prior radiotherapy and surgery for basal cell carcinoma of the external nose. Post-operative follow up ranged from 6 months to 22 years, with a mean of 8.4 years. Of the 87 patients who underwent bilateral closure, 79 (91 per cent) achieved complete cessation of bleeding. Epistaxis score as proposed by Al-Deen and Bachmann-Harildstad[57] was available for 50 of the patients who underwent bilateral closure. It dropped from a mean of 9.42 pre-operatively to 0.54 post-operatively, with a high effect size indicating substantial improvement. Common post-operative complaints included decreased sense of smell and taste (40 per cent), fatigue (14 per cent), sleep disturbances (12 per cent) and ear fullness (10 per cent). Nasal obstruction was less common (14 per cent) and some patients required additional treatments for mouth dryness (10 per cent). In addition, 12 per cent of patients mentioned embarrassment even though the closure was not usually visible. Every patient interviewed indicated that they would choose to undergo the procedure again and would recommend it to others in similar situations.[58]

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In a case report, a patient had an epistaxis episode despite Young's procedure. Even with bilateral embolisation, haemostasis could not be achieved. Reversal of Young's procedure had to be performed so traditional packing could be done.[59]

- Hereditary haemorrhagic telangiectasia is a genetic vascular disorder with recurrent epistaxis, anaemia and decreased quality of life that is prevalent in Afro-Caribbean populations of the Netherlands Antilles
- The Curaçao criteria are essential for diagnosis
- Self-treatments such as nasal packing, occlusion and topical oils vary in success; bevacizumab and intranasal tranexamic acid sprays are less effective
- Submucosal bevacizumab injections are a promising, minimally invasive option for managing epistaxis, balancing efficacy with manageable side effects, but further research is needed
- Intravenous bevacizumab and tacrolimus improve epistaxis and haemoglobin levels; pazopanib shows dramatic improvement in refractory cases
- Effective surgical interventions include laser therapies, coblation, septodermoplasty, super-selective embolisation and bilateral nasal closure, with laser therapy most recommended

Conclusion

Almost all patients with hereditary haemorrhagic telangiectasia will suffer from epistaxis that could range from mild to severe and life-threatening. The disease is progressive, hence the importance of a stepwise approach. Simple measures such as topical oils can be efficient. More disease-specific medical therapy, such as bevacizumab injections, offers a balance between efficiency, ease of access and side effects. However, data in the literature are limited because of the rare nature of the disease. When surgical intervention is indicated, the consensus in the literature is to rely on laser therapy, although bipolar cautery is a reasonable option. As a last resort, surgical closure of the nasal cavity is a highly efficient treatment accepted by a carefully selected group of patients.

Competing interests. None declared

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