ORIGINAL CONTRIBUTION

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Percutaneous embolization on hereditary hemorrhagic telangiectasia patients with severe epistaxis*

S.J. Braak[1], C.A. de Witt[2], F.J.M. Disch[2], T.Th.C. Overtoom[1], J.J. Westermann[3]

[1] Department of Radiology, St Antonius Hospital, Nieuwegein, The Netherlands
[2] Department of ENT, St Antonius Hospital, Nieuwegein, The Netherlands
[3] Department of Pulmonology, St Antonius Hospital, Nieuwegein, The Netherlands

SUMMARY

Objectives: *To evaluate the results of embolization in patients with hereditary hemorrhagic telangiectasia (HHT) because of severe epistaxis.*

Methods: *All HHT patients who underwent an embolization (between 1992 and 2006) were asked to participate in this retrospective study. Twelve patients who had in total 19 embolization procedures were interviewed. A questionnaire was used assessing the frequency, severity, duration of epistaxis and their Impact on Lifestyle (IoL). Haemoglobin values were collected from the patients' records. Embolization of the pathologically enhancing lesions was performed using PVA particles.*

Results: *The direct effect of the embolization is very good in 95% of patients. The Impact factor (daily frequency x severity) of epistaxis improved in the first month ($p = 0.000$) and one year after embolization ($p = 0.009$). Eleven embolizations (61%) were still associated with significant improvement. There was a reduction in the duration of epistaxis by 16 minutes per day one month after embolization ($p = 0.005$). However, this reduction was not found one year after embolization. Mean haemoglobin rose significantly after 1 year by an average of 0.8 mmol/l ($p = 0.045$). Impact on Lifestyle improved in 68% of the procedures and was unchanged in 32%.*

Conclusion: *Embolizations remain a therapeutic option in experienced hands. The indication should be made carefully, because of possible (major) complications.*

Key words: Embolization, hereditary hemorrhagic telangiectasia, epistaxis, Impact factor, Impact on Lifestyle, complications

INTRODUCTION

Hereditary hemorraghic telangiectasia (HHT) is an autosomal dominant vascular disease, characterized by mucocutaneous telangiectases, epistaxis, and visceral arterioveneous malformations [(1)].

The prevalence of HHT is estimated at 1:10,000; however, the highest point prevalence in the world is 1:1.331 in inhabitants of Curaçao and Bonaire older than 12 years [(2)]. Most cases of HHT are caused by mutations of the gene for endoglin *(ENG)* on chromosome 9 *(HHT-1)* (OMIM # 187300) or for activin-like receptor kinase I *(ALK-1)* on chromosome 12 *(HHT-2)* (OMIM # 600376) [(3)].

The diagnosis is definite if three of the Curaçao criteria (recurrent epistaxis, mucocutaneous telangiectases, visceral lesions and family history) are present [(4)]. A diagnosis of HHT cannot be established in patients with only two criteria, but should be recorded as possible or suspected to maintain a high index of clinical suspicion. If fewer than two criteria are present, HHT is unlikely, although children of affected individuals should be considered at risk in view of age related penetration in this disorder [(4)]. Epistaxis is the most common symptom in HHT and occurs in 90-96% [(5)].

Epistaxis occurs on two different sites: anterior and posterior nose. Anterior nosebleeds are situated on the nasal septum known as locus Kiesselbach's plexus. This is an anastomosis of three primary vessels: anterior ethmoidal artery (branch of the ophthalmic artery), sphenopalatine artery (branch of the maxillary artery) and small branches of the facial artery. Posterior nosebleeds arise from the posterolateral branches of the sphenopalatine artery. Both the maxillary artery and the facial artery originate from the external carotid artery. The ophthalmic artery is a branch of the internal carotid artery.

The telangiectases are most frequently found on the lips, tongue, nasal septum and turbinates [(5)]. Epistaxis usually starts in childhood and increases with age. In addition to epistaxis, symptoms may be present due to visceral involvement.

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There are many treatment modalities to control epistaxis in HHT. These include chemical or electrocautery, laser photocoagulation, septodermoplasty, microvascular free flap, regional facial cutaneous flap, modified Young's procedure, medical treatment, surgical ligation, Ross operation and embolization [6,7].

Therapeutic embolization of the nasal blood circulation was first described in 1974 by Sokoloff et al. [8] Several small studies followed, but most of these show only temporarily subjective effects [9-13].

The goal of the present study is to investigate and measure the results of embolization on epistaxis in patients of the Dutch HHT clinic.

MATERIAL AND METHODS

Population

Between November 1992 and October 2006 eighteen patients underwent 28 percutaneous embolizations for severe epistaxis, not responding to any previous treatment. All patients met the newly proposed Curaçao criteria for HHT. Five patients were excluded; three patients died of unrelated causes. Two patients were not cooperative. In this study 13 (72% follow up) patients were included with written informed consent. The study was approved by the Ethical Committee of the St. Antonius Hospital, Nieuwegein, the Netherlands. One patient was not included in the one month and one year follow-up because this patient died of a major brain infarction following the embolization. This patient is included in the complication rate. The remaining 12 patients underwent 19 procedures; all procedures were carried out by one experienced interventional radiologist (TO). Eight patients were known with HHT-1 and 4 with HHT-2. There were 19 embolization procedures because of recurrence in 4 patients. Acute embolization was done on 2 patients because of intractable bleeding. All patients had been treated before, the majority (83.3%) with multiple modalities. Sixty-seven percent had received medications, 92.7% were once or more coagulated or received laser treatment and 75% underwent (multiple) operations. Saunders dermoplasty was only performed on 2 patients.

A telephone questionnaire was done by two observers (SB, CW) to obtain retrospective information about the daily frequency (number of epistaxis per day), severity (measured in 3 ordinal scales: dripping, spout or gush), duration of the epistaxis in minutes, impact on lifestyle (IoL) and complications. Hemoglobin level (Hb) was collected by reviewing the patients' hospital electronic record or by the information sampled by the patients general practitioner. These questions and collected information concerned a period of 1 month before embolization, 1 month and 1 year after. However Hb referred to values only 1 month before and 1 year after embolization.

The influence of the nosebleeds on the patients' lifestyle was quantified into four grades: none or very little impact; mild, (described as bothersome but without influence on normal activity); moderate, (influencing normal daily activity) and severe, (making normal daily activities impossible) [1]. To measure the effect of the embolization an impact factor (IF) was used, defined as daily frequency x severity (in 3 grades), as well as Hb and IoL. IoL was only measured one month before and one year after the procedure.

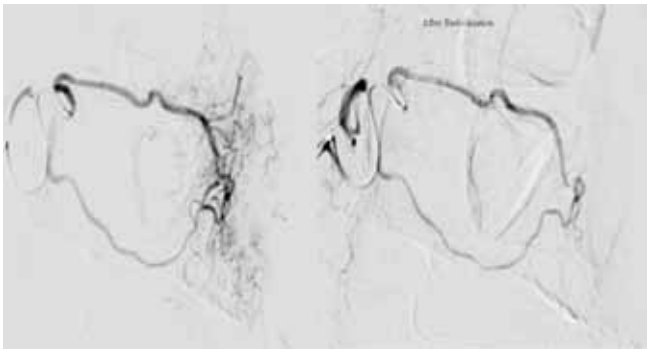

Figure 1. The a. maxillaris internal before and after embolization.

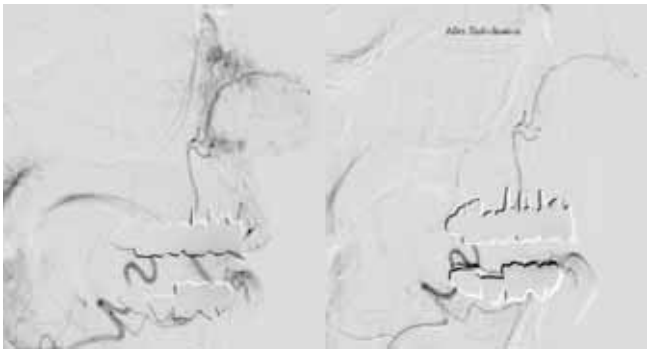

Figure 2. Collateral formation of the a. facialis before and after embolization.

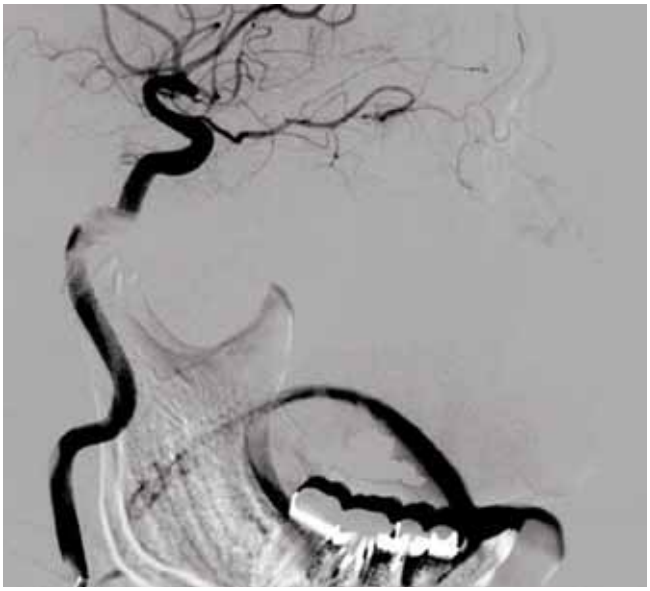

Figure 3. Collateral formation of the a. opthalmica. In this study no selective embolization was done here.

Methods

The embolizations were performed under local anaesthesia. The femoral approach was used in all cases. Prophylactic

Table 1. Baseline characteristics (n=12).

n=12	Mean	SD
Frequency (times per day)	4.3	2.2
Severity (1 = dripping, 2 = spout, 3 = gush)	2.4	0.7
Duration (minutes)	24.9	16.3
Hemoglobine (mmol/l)	6.4	1.3
Impact on Lifestyle (1 = none, 2 = mild, 3 = moderate, 4 = severe)	3.3	0.8

heparin was not given. Diagnostic angiography was done by nonselective studies (aortic arch) followed by selective studies at the site of the epistaxis (common carotid artery, external carotid artery and/or internal carotid artery), using a 4 of 5 F catheter and microcatheters, to localize the site of pathological enhancement and collateral feeders. Then superselective studies of the two major branches of the external carotid arteries (maxillary artery and the facial artery) were done. Embolization was only done in the pathological areas, usually distally in the maxillary artery and sometimes in the facial artery, as close to the nidus as possible and distally from connections to the ophthalmic artery. The embolic material in all patients was polyvinyl alcohol particles (PVA). The size of the PVA particles ranged from 150-450 μm. The PVA particles mixed with contrast were slowly injected superselectively, followed by superselective control injections until the desired result. Non-selective control angiography was performed after embolization by more proximal contrast injections in the maxillary artery, facial artery and internal carotid artery to exclude collateral feeders. The ophthalmic artery was never embolized, not even when it had taken over the vascularity after embolization.

Statistical analysis

Statistical analysis was performed using the statistical analysis program SPSS version 15.0.

The magnitudes of the differences between daily frequency, severity, duration, IoL, IF and Hb before and after embolization were analyzed by the Wilcoxon Signed Ranks test. The differences were considered significant for 'p' values less than 0.05.

RESULTS

Six (50%) of the 12 patients were female. The mean age at the time of the embolizations was 55.4 year (SD 1.62 year). The baseline data of the study population are shown in Table 1.

All patients were treated in case of abnormal angiography, abnormal mucosal blush and/or mucosal telangiectasis. Four patients (33.3%) underwent multiple embolizations. The immediate angiographic result was good (Figure 1).

In 6 (31.5%) of the embolizations there was (some) takeover by other vessels (facial and/or ophthalmic artery) of the vascularization. The facial artery took over in 3 embolizations. In 2 embolizations the ophthalmic artery took over the vascularization and in 1 embolization there was collateralization by both the facial artery and the ophthalmic artery. Embolization of the collateralization of the facial artery was only done when there was significant takeover (Figure 2). The collateralization of the ophthalmic artery was not embolized because of high risk (Figure 3). Fifty-eight percent of all patients had treatment after embolization(s). Fifty-seven percent of these patients were treated once or more with argonplasma, 71% were coagulated, 14% underwent Saunders dermoplasty and 29% a septalplasty.

Impact factor, hemoglobine and duration

IF of the entire group decreased from 10.9 (95% CI 7.7-14.0) to 3.4 (95% CI 0.9-5.9) (p = 0.000) after 1 month and from 10.9 (95% CI 7.7-14.0) to 7.0 (95% CI 3.9-10.1) (p = 0.009) after one year (Table 2). Categorizing the embolizations into treatment frequency all, except the forth embolization treat-

Table 2. Difference (Δ) of the mean impactfactor, hemoglobine and duration of nosebleeds after 1 month and 1 year. # means no data available because no 1 year follow-up. (* = significant ($p < 0,05$), ^{ns} = non-significant).

	Δ IF	**Δ IF**	**Δ hb (mmol/l)**	**Δ hb (mmol/l)**	**Δ duration (min)**	**Δ duration (min)**
	1 month	1 year	1 month	1 year	1 month	1 year
1st embolization (n=12)	–5.4*	–2.8*	0.2 ^{ns}	1.0 ^{ns}	–7.96 ^{ns}	–2.29 ^{ns}
2nd embolization (n=4)	–9.3*	–6.1*	0.1 ^{ns}	0.8 ^{ns}	–13.5 ^{ns}	–11.13 ^{ns}
3rd embolization (n=2)	–11.0 ^{ns}	–2.8*	0.6 ^{ns}	–0.1 ^{ns}	–40.03*	27*
4th embolization (n=1)	–21.8 ^{ns}	#	1.2 ^{ns}	#	–75.0 ^{ns}	#
Total (n=19)	–7.5*	–3.9*	0.2 ^{ns}	0.92*	–16.03*	–12 ^{ns}
Patients with only 1 embolization (n=8)	–4.4*	–1.9 ^{ns}	–0.2 ^{ns}	0.9 ^{ns}	–11.8 ^{ns}	–3.8 ^{ns}
Patients with 2 or more embolizations (n=4)	–9.7*	–5.4*	0.3 ^{ns}	0.9 ^{ns}	–13.6 ^{ns}	1.2 ^{ns}

Table 3. Individual Impactfactor (IF) before and after embolizations. NA = not available.

Patient	Embolization #	Frequency	Severity	IF	Frequency	Severity	IF	Frequency	Severity	IF
		before			after 1 month			after 1 year		
1	**1**	2	1	**2**	3	1	**3**	2	2	**4**
2	**2**	6	3	**18**	3,5	2	**7**	6	3	**18**
3	**3**	2,5	3	**7,5**	1	3	**3**	2,5	3	**7,5**
4	**4**	2,5	3	**7,5**	1,5	1	**1,5**	2,5	1	**2,5**
5	**5**	9,5	2	**19**	2	2	**4**	9,5	2	**19**
	6	6	2	**12**	1	1	**1**	3	3	**9**
6	**7**	2	1	**2**	0,03	1	**0,03**	0,07	1	**0,07**
	8	5,5	2	**11**	0,03	1	**0,03**	0,03	1	**0,03**
	9	5,5	3	**16,5**	0,07	1	**0,07**	5,5	3	**16,5**
	10	7,5	3	**22,5**	0,25	3	**0,75**		too early	
7	**11**	3	2	**6**	0,03	2	**0,06**	0,03	2	**0,06**
	12	4,5	3	**13,5**	1,5	2	**3**	2	2	**4**
8	**13**	1,5	3	**4,5**	0	0	**0**	1,50	2,0	**3**
9	**14**	7,5	3	**22,5**	7,5	3	**22,5**	5	3	**15**
10	**15**	5	3	**15**	2,5	3	**7,5**	4	3	**12**
11	**16**	2,5	2	**5**	1	1	**1**	3	2	6
	17	2,5	2	**5**	1	1	**1**	2	2	**4**
	18	3,5	2	**7**	1,5	1	**1,5**	1,5	1	**1,5**
12	**19**	3,5	3	**10,5**	2,5	3	**7,5**	3,5	3	**10,5**
13	**20**	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mean total		**4.3**	**2.4**	**10,9**	**1.6**	**1.7**	**3,4**	**3.0**	**2.2**	**7,37**

ment, showed a significant decrease in IF (Table 2). Individually, there was improvement of the IF after 1 month in 18 of the 19 procedures, and in 11 of the 18 procedures, that could be evaluated, after 1 year. The IF ranged from 0 to 22.5 (Table 3). Patients who needed only one embolization treatment showed a decrease in IF after one month from 10.9 (95% CI 5.1-16.8) to 6.5 (95% CI 0.59-12.4) (p=0.015). However, this decrease disappeared after one year 10.9 (95% CI 5.1-16.8) to 9.1 (95% CI 4.2-13.9) (p=0.134). The IF of the patients needed multiple treatments decreased after one month and one year; from 10.9 (95% CI 6.5-15.3) to respectively 1.13 (95% CI 0.26-2.0) (p=0.000) and 5.5 (95% CI 0.94-10.0) (p=0.027) (Table 2).
The patients who needed multiple embolizations the IF did not correlate with the need of multiple procedures.

The mean Hb improved from 6.4 mmol/l (95% CI 5.7-7.0) to 7.2 mmol/l (95% CI 6.3-8.1) (p = 0.045) after one year. The mean duration of epistaxis after one month was shorter (24.9 min (95% CI 14.9-34.9) vs 10.7 min (95% CI 3.8-17.5) (p = 0.005), but not significant after one year (24.9 min (95% CI 14.9-34.9) vs 22.5 min (95% CI 5.3-39.6) (p = 0.372) No significant changes in Hb or duration are noticed in the subgroups (Table 2).

Impact on Lifestyle
IoL after one year was better in 12 procedures (63%) and was equal in the remaining 7 (37%). The mean score (on a scale of 1 to 4) before embolization was 3.3 (95% CI 2.9-3.7); one year after the embolization procedure the mean score was 2 (95% CI 1.5-2.5). The IoL improved significant (p=0.000). In 79% the IoL was moderately or severely impaired before embolizations, and in only 21% after the procedure (Table 4).

Complications
Two patients (10% of the 20 procedures) had temporary facial pain most likely because of mucosal ischemia. One patient (3.6% of the 28 embolizations) died of a major brain infarction following the embolization.

DISCUSSION

Therapeutic embolization is effective in 80-93% in idiopathic epistaxis and epistaxis due to trauma or tumour [11,14]. Elective embolization in patients with HHT is less promising. Previous studies in small numbers of patients describe variable results. Parnes et al. embolized 4 HHT patients [10]. One patient slightly improved, one felt epistaxis was worse after embolization.

Table 4. Impact on Lifestyle (IoL) before and after embolizations.

n=12	Embolization	
	Before	After 1 year
IoL		
(1) None		31.6%
(2) Mild	21.1%	47.4%
(3) Moderate	31.6%	10.5%
(4) Severe	47.4%	10.5%
Mean (SD)	3.3 (0.8)	2.0 (0.94)

Two other patients experienced no change following treatment. Elden et al. embolized 16 HHT patients [12]. He had a 100% success rate 1 week after embolization, a long-term improvement of 30% and a long-term result of 17% in case of an elective embolization. Fisher et al. treated 8 patients [13]. Two patients showed long-term improvement. They suffered fewer nosebleeds than before. Layton et al. embolized 12 patients with HHT [11]. Fifty-eight percent required surgery and/or re-embolization, 25% underwent a single procedure cure, 17% continued to have severe epistaxis.

The present results compare favourably with these studies. The IF (daily frequency x severity) and duration of nosebleeds had significantly improved one month after embolization. After one year, still a significant improvement was seen of the IF, level of hemoglobin and IoL. The influence of the nosebleeds on the patients' lifestyle was moderate/severe in 79% before treatment and in only 21% one year after embolization. A single procedure was sufficient in this series in 63%, but 37% required two or more embolizations.

However, the study has several shortcomings. The number of patients is small due to the relatively rare indication of embolization. The data were collected retrospectively by a questionnaire. Also, not all patients had been treated with the most promising procedure at present: Saunders septodermoplasty with Ross modification. This technique dates back only a few years. The Ross modification is a new operation on patients with intractable nosebleeding. A septectomy, turbinectomy and radical excision of all mucosal lining in the nasal cavity is performed. The perichondrium and periostium is then covered with a split skin graft.

Regarding the IF there were two failures one month after the 19 embolizations, patient 1 and 9 (Table 3). Embolization was incomplete in six (32%) cases due to collateral vascularization, that was not embolized because the ophthalmic artery was involved or because there was a non-significant takeover by the facial artery. The two failures belonged to this group. After one year the results were less good: seven of the 18 procedures did not lead to a sustained improvement of the IF (Table 3). Recanalization of the embolized arteries or newly formed telangiectasia are the probable mechanisms.

The procedure was well tolerated and there were only two minor and transient complications in the present series due to mucosal ischemia. However, one patient excluded from the complete follow-up series died of a cerebral infarction following the embolization. This 60-year-old patient was embolized at the left side and developed an infarction controlateral after an injection of contrast in the right common carotid artery. It can be hypothesized that this complication was not related to the embolization per se, but to a thromboembolus from the guiding catheter and thus to carotid angiograph in general. In general no contrast injections during epistaxis embolizations are performed in the controlateral side. Prophylactic heparin was not used. To the best of our knowledge only Layton et al. used routinely prophylactic heparin [11]. Elden et al. used prophylactic heparin in 2 out of 108 procedures [12]. Our patient did not suffer from previous transient ischemic attacks. It is reasonable when a procedure is performed because of intractable epistaxis, thromboembolic prophylaxis is not recommended, but in all other indications you should give heparin to prevent thromboembolic events by giving a bolus of 2,500-5,000 U heparin. The effect will be a longer embolization time and possible uncontrollable overembolization because the direct embolization effect of the PVA particles is changed with the risk of injecting to much PVA particles.

CONCLUSION

Embolization of the nasal arteries remains a therapeutic option in experienced hands, when all modern medical and surgical modalities have failed to reduce severe nosebleeds in HHT. It may also be done in cases of acute intractable epistaxis, for instance to create the opportunity for surgical interventions.

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Drs. S.J. Braak MD
St. Antonius Hospital
Department of Radiology
PO Box 2500
3430 EM Nieuwegein
the Netherlands

Tel: +31-6-47314316
E.mail: sjbraak@gmail.com