Local sclerotherapy with Polydocanol (Aethoxysklerol®) for the treatment of Epistaxis in Rendu-Osler-Weber or Hereditary Hemorrhagic Telangiectasia (HHT): 15 years of experience*

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Summary

Hereditary Haemorrhagic Telangiectasia or Rendu-Osler-Weber syndrome is a rare autosomal dominant vascular disease characterized by mucocutaneous and gastrointestinal telangiectases and localized arteriovenous malformations in lung, brain and liver.

Epistaxis, due to rupture of telangiectases of the nasal mucosa, is the most frequent clinical manifestation, leading in many cases to severe impairment of the quality of life in the patients.

Though several treatments have been used to reduce epistaxis, none have been completely effective, with the exception of polydocanol (Aethoxysklerol®) in submucosal or subpericondrial injections, which was first presented in 2000 with very good results.

After fifteen years using polydocanol in submucosal injections on 45 patients and with nearly 300 injections, we have observed that in 95% of all cases, their nose bleeds improved with respect to frequency and quantity without any important side effects. There was just one case of septal perforation, another with increased septal perforation, and one patient who suffered from dizziness and blurred vision for a few minutes. In this paper the results obtained using this technique over a fifteen-year period will be presented and evaluated.

Key words: hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber, epistaxis, polydocanol, submucosal injection

Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler-Weber is a multisystemic disease with an autosomal dominant inheritance pattern and increased penetrance with age [1-3]. It was first described by Sutton in 1864, and described as a new disease different from hemophilia in 1896. Osler and Weber each published their first reports in 1901 and 1907 respectively. The term 'Hereditary Hemorrhagic Telangiectasia' (HHT) was given by Hanes in 1909. Prevalence is estimated to be approximately 1:5000-8000 inhabitants, with a certain degree of variability depending on geographical areas [3-5]. Although there are at least 5 genes which can cause HHT clinical symptoms by mutation, 90% are related with mutations in *Endoglin,* on chromosome 9 or *ALK1/ACVRL1* encoded on chromosome 12, leading to HHT1 and HHT2, respectively. Other mutations have been identified in

Smad4 (2%), causing the Juvenile Polyposis and Hemorrhagic Telangiectasia syndrome (JP-HHT). Moreover, mutations in two loci of chromosomes 5 and 7 are responsible for HHT3 and HHT4, but these genes have not yet been identified [6,7]. The mutations lead to vascular malformations in different locations, such as telangiectases in the nasal and gastric mucosa and arteriovenous malformations in liver, lungs and brain.

Epistaxis or nose bleeding is the most frequent clinical manifestation in HHT, but with variable intensity, appearing in 93% of HHT patients, 90% before the age of 21. Epistaxis results from ruptures of telangiectases present in the nasal mucosa, leading when severe, to recurrent visits to emergency units, periods in hospital and transfusions, thereby, endangering the physical integrity of patients and reducing their quality of life. To prevent a subjective

perception of epistaxis, Bergler et al., [8] established a graded scale to classify nose bleeds, both in intensity and frequency. However, epistaxis is not the only clinical symptom of these patients. The disease is a perfectly established syndrome with clear clinical diagnostic criteria, known as the Curaçao criteria [9].

Treatments used in the natural history of this disease, have varied greatly, from mere packing, to selective and supraselective embolizations, including chemical cauterizations, laser and argon. In 2000, the use of polydocanol in submucosal infiltrations for the management of epistaxis was published for the first time [10]. This treatment has been used for the past 15 years in a total of 55 patients, among them 45 with HHT, the rest being affected by different ENT pathologies [11]. The number of injections given was 245, and no serious complications were observed during those years. In this manuscript we intend to demonstrate the efficacy and safety of this treatment in a sufficiently large number of cases to allay any fear triggered by previous publications where alternative products were used [12-15].

Material and methods

From 1996 to 2010, a total of 45 patients diagnosed with Rendu-Osler-Weber syndrome, based on the clinical Curaçao criteria, were treated in the ENT unit of Valladolid University Hospital, Spain.

Technical description of the procedure

- Prior anesthesia of the nasal area to be treated, with a tetracaine plus adrenaline- cotton plug embedded in the nasal cavity for 10 minutes.
- 0.5% Polydocanol, also known as Lauromacrogol 400 (0.5% Aethoxysklerol®) (Kreussler Pharma, Ferrer Farma S.A, Spain) was used.
- 1 - 2 ml of Aethoxysklerol® infiltration in the septum or in the telangiectasia area, in the submucosal and/or subpericondrial region with a 25 gauge needle (Spinocan). We only performed infiltrations in one nasal cavity, never bilaterally at the same time.
- Hemostasis in the treated area was carried out with tetracaine + adrenaline. Exceptionally, Espongostan (gelatine sponge) or Surgicel were used to stop the post-infiltration hemorrhage.
- One month after the first infiltration, and depending on the response to the treatment, infiltrations would continue either in the same nasal cavity or switch to the other. The injections would be continued on a monthly basis until the epistaxis was controlled (infrequent and less intense nose bleeds). Afterwards infiltrations would be 'on demand,' when patients were again suffering from epistaxis.

Statistic analysis

The statistical analysis was done using the SPSS statistical package for social sciences, 15.0 version. The quantitative variables are shown as plus or minus averages and the qualitative as well as the standard deviation (SD) as frequency distributions. To compare the EUROQOL-5D results before and after treatment, the Wilcoxon test was applied.

Results

A total of 45 patients with ages ranging from 12-84 years (average 59.98 ± 14.5) were included in the study. Among them, 26 were males (57.8%) with a mean age of 57.31 ± 14.4 years and 19 females (42.2%) with a mean age of 63.63 ± 14.5. In our population, 75.5% started to suffer from epistaxis before they were 20 years old and the remaining 24.5% after this age.

The frequency and intensity of epistaxis (Bergler et al., [8], Table 1) in all our patients corresponded with grades 2 and 3 for frequency and grades II and III for intensity, with the 3/III combination being the most common (Table 2).

Table 3 gives a breakdown of the different treatments previously received by the patients, showing that most patients were treated with nose packages, chemical cauterization, and selective embolizations. As can be seen from Table 3, the combinations of these treatments vary, since patients have been treated by multiple and different therapeutic procedures. In the column marked 'Others,' we have included two patients who had previously been unsuccessfully treated with Ethybloc®, and one patient treated with Ethoxysclerol® 6 years ago, with good results but requiring new infiltrations, due to epistaxis. We have not included pharmacological treatments with antifibrinolytics or topical oestrogens in the table.

Among the patients, 51.1%, had been given blood transfusions, but these have not been recorded as we do not consider them relevant to this study.

The number of Aethoxysklerol® infiltrations is shown in Table 4, where it can be seen that 51.1% of the patients received between 1 and 4 injections, while the remaining 48.9% received 5 or more. The average number of infiltrations per patient is from 5 to 6 in each nasal cavity. However, over the past 15 years some patients have received up to 16 or 18 injections, if both nostrils are taken into account (Table 4).

From Table 5 'Complications', it is evident that the vast majority of patients, as many as 42, (93.3%) did not suffer any side effects after the injections. One patient suffered a septal perforation, and in another patient, with a previous septal perforation, it became slightly enlarged. Finally, one other patient felt dizzy and had blurred vision for a few minutes after the injection, but these symptoms disappeared soon after, without any sequelae (Table 5).

Regarding treatment efficacy, the bleeding decreased in frequency and amount to a grade combination of 1/I in most

Table 1. Grading of frequency and intensity of nasal bleeding [8].

Frequency of Bleeding		Intensity of Bleeding	
Grade 1	Less than once per week	Grade I	Slight stain on handkerchief
Grade 2	Several times per week	Grade II	Soaked handkerchief
Grade 3	More than once per day	Grade III	Bowl or similar utensil necessary

Table 2. Distribution of patients according to the Bergler/Sadick scale of epistaxis.

	Frequency		Intensity		Combination of degrees		
Degree	Nº	%	Nº	%	2/II	10	22.2 %
1/I	0		0		2/III	5	11.1 %
2/II	15	33.3	14	31.1	3/II	4	8.9 %
3/III	30	66.7	31	68.9	3/III	26	57.8 %

patients (73.2%), which means less than one bleeding per week, or in other words just a few blood spots on a handkerchief. A good response was observed in 21.9% of the patients where the bleeding decreased to grade 1-2/I-II, meaning that the patients might experience either the occasional haemorrhage soaking of a handkerchief, or just light bleeding more than once a week with only discrete stains on a handkerchief. Though there was no response in 2 patients (4.9%) and the response could not be recorded in 4 patients (8.9%), none of them worsened (Table 6). Discarding the 4 uncontrolled patients, the level of satisfaction was measured in the remaining patients by a questionnaire and the percentage calculated based on the remaining participants. Of the patients, 75.6% were very satisfied, 19.5% were quite satisfied, and 4.9% reported no change in satisfaction. None felt any worse (Table 6).

The quality of life test, Euroquol-5D, was also applied, revealing a significant improvement in daily activity as well as considerable relief from pain and discomfort, and especially depression and anxiety (Table 7).

Discussion

The treatments used to stop or prevent epistaxis are diverse, each with different degrees of success [16-18]. Patients are often the experts, knowing the best way to stop epistaxis, based unfortunately on their current situation. For this reason, it is important to let them help us when they are admitted to hospital, because they are fully aware of their condition, and neglecting a patient's advice may lead us into a difficult and frightful situation. Sometimes, they tell us of types of food that trigger epistaxis, and we suspect that this is due in some measure to the salicylate content of certain foodstuffs. For this reason, prescribing anticoagulants or platelet antiaggregants (recommended for other people from a certain age on) should be carefully considered, evaluating risks against benefits [16].

Topical treatments with humidifiers, Vaseline, and oestrogen-containing ointments are also used by HHT patients with different results. Nose packing material has evolved in recent years, changing from gauze placed under pressure in the nostril to the introduction of neumopacking, sometimes embedded in procoagulant ointments to avoid bleeding after removal, such as Rapid-Rhino®.

Pharmacological therapy has made use of aminocaproic and tranexamic acids [18], oestrogens and oestrogen receptor modulators (tamoxifen and raloxifene), antiangiogenic drugs (Bevazicumab, Thalidomide, Interferon alpha or beta), immunosuppressors and iron supplements, some of them with promising results, others acting as coadjuvants.

Chemical cauterizations are not very efficient, and the electric scalpel systematically gives rise to septal perforations. However, laser in association with topical oestrogens is undoubtedly efficient [19], but as with the electric scalpel, may occasionally lead to septal perforations [20] and the treatment must be performed in a surgical environment under general anaesthesia.

More aggressive surgical techniques, such as septodermoplasty [21], Young's occlusion [22] to avoid the aggression of air passing through the nose, the selective/supraselective embolizations or arterial ligations are reserved for patients that do not respond

Table 3. Previous treatments received.

	NP		CC		EB		L		SR		SE		VL		D		Others	
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
45	100	43	95.5	9	20	8	17.8	2	4.4	15	33.3	2	4.4	5	11.1	3	6.6

NP (Nose Packages); CC (Chemical Cauterization); EB (Electric blade); L(Laser); SR (Submucous resection); SE (Selective Embolization); VL (Vascular Ligation); D (Dermoplasty); Others.

Table 4. Treatment with Aethoxysklerol®.

No. of inflitrations		No. of nostrils infiltrated		No. of infiltrations according to the Bergler/ Sadick (average)	
1-4 doses	51.1 %	One Nostril	16 (35.6%)	2/II	6.2
				2/III	6.2
≥ 5	48.9 %	Both Nostrils	29 (64.4%)	3/II	4.75
				3/III	5.12

to other techniques. Among them, the most efficient are the embolizations, although they tend to recanalize in time. We have observed several cases, where the embolization instead of decreasing epistaxis, worsened it. In relation to dermoplasty, we should mention that its effect, in many cases, is similar to that of the occlusive technique, decreasing the nostril lumen or even closing it, which makes it difficult to apply packaging techniques when haemorrhages occur behind the valve.

Sclerotherapy, using different compounds has also been used to treat epistaxis in HHT [10-15]. We have had no experience using Ethybloc®, since it was not available to us, but according to the publications we have reviewed [14,15], it must be administered with general anesthesia therefore repeating the treatment would be complicated with the added risk of the anesthesia.
Fibrin glue (Tissucol®) has also been used [12,13] but serious hypersensitive side effects associated with its administration [13] even hemiplexia [12] have been reported. We have used Tissucol® on two occasions in operations without positive results; moreover, it is difficult to handle. In view of the aforementioned problems and side effects, it does not seem to be a recommendable treatment.

Polydocanol or Lauromacrogol 400, is an acrylic compound of 600 MW, which has a selective effect on the venous endothelium, leading to a secondary thrombosis without necrosis in the surrounding tissue providing this is healthy and well irrigated. The septal perforation in simultaneous bilateral infiltrations was an exceptional side effect, only observed in one case, and that could have been due to poor mucosa irrigation, which is quite frequent in the damaged nostrils of these patients. As it is a stable compound at room temperature and has low viscosity, its administration is very simple and efficient in intralumen, submucosal or subpericondrial injections. It is commercially available as Aethoxysklerol® (Kreussel Pharma) and comes in boxes containing five 2 ml vials. We use vials of 0,5 % that contain 10 ml ethanol and 10 mg of polydocanol. 2 and 3% are also available, increasing the amount of polydocanol to 40 and 60 mg respectively in the same volume of ethanol [9]. For HHT purposes, we have used 0.5% in accordance with previous reports on varicous vein treatments [9].

We have treated 45 patients with Aethoxysklerol®, giving 245 infiltrations with highly satisfactory results, as far as control of frequency and intensity of epistaxis are concerned. This technique is recommended for HHT due to its relatively easy application (whenever possible without the interference of haemorrhages or nose packing) and only needs local anaesthesia. Moreover, in those patients where the technique cannot be applied with local anaesthesia, injections can be carried out under total anaesthesia, though we have not needed to employ this option so far. Some of the problems related to the technique include the presence of crusts interfering with visibility, previous perforations, or the inexistence of septal cartilage to hold the infiltration needle and, of course, the immediate bleeding following the initial application. Nonetheless, in spite of these problems, all the patients were treated with the exception of two with per-

Table 5. Complications.

	Frequency	Percentage
No complications	42	93.33
Foramen postinfiltration	1	2.22
Enlargement of previous foramen	1	2.22
Dizziness and blurred vision	1	2.22
Not evaluated	4	8.9
Total	45	100.0

Table 6. Efficiency and treatment satisfaction.

	Efficiency			Satisfaction		
	Nº	%	% valid(*)	Nº	%	% valid (*)
Worse						
Equal	2	4.4	4.9	2	4.4	4.9
Good	9	20.0	21.9	8	17.8	19.5
Very Good	30	66.7	73.2	31	68.9	75.6
No Evaluated	4	8.9		4	8.9	
Total	45	100	100	45	100	100

(*) Non evaluated patients are not contabilized.

manent packages, which impeded application. These two cases have been placed under 'Equal' in Table 6.

The results obtained are very satisfactory with up to a 95% improvement in effectively controlling epistaxis, as well as a high level of patient satisfaction. The two patients shown as 'Equal' are the patients whose treatment could not be applied either because of continuous hospitalization in one case, or due to continuous nose packages in the other. Four patients could not be localized (Table 6). All the treated patients were satisfied because the severity of their epístaxis was reduced to such an extent that there was an overall general improvement, specifically with regard to their anaemia and associated asthenia as well as the reduced need for transfusions and visits to the hospital. These parameters have not been statistically evaluated in this study. The quality of life questionnaire clearly indicates an improvement after Aethoxysklerol® treatment, especially concerning anxiety and pain in these patients. As far as mobility and personal care are concerned, both the ageing process and the global nature of the question must be taken into account (Table 7).

We should clarify that this treatment is not a definite cure. Despite telangiectasia removal with this technique, the genetic impairment in these patients means that, these will reappear. However, follow-up treatments with Aethoxysklerol® are much easier than at the beginning of treatment. As stated in the Material and Methods section, once the patients are controlled with Aethoxysklerol® infiltrations, the successive infiltrations are 'on demand' depending on their symptoms.

Regarding the side effects of the technique, we have only recorded one septal perforation, which can be explained by the fact that two simultaneous infiltrations were made on both sides of the nasal wall. In another case, we have shown an enlargement of the preexisting perforation resulting from previous treatments. We cannot explain the observation of a short period (3 - 4 minutes) of dizziness and blurred vision in a patient following the infiltration. We have not observed this effect in other patients, not even in this patient who was subjected to posterior infiltrations.

The first patients to be treated were recruited from ENT external consultations. Afterwards, the main source of patients was through the Spanish HHT Association. The periodical patient meetings organized by the association are where patients can speak about their experiences and treatments. Sierrallana Hos-

Table 7. Euroqol-5D Questionnaire (Likert Scale).

	Before		After		p**
	Average	Standard Deviation	Average	Standard Deviation	
Mobility	1.07	0.385	1.12	0.431	0.317
Personal care	1.07	0.267	1.08	0..400	1.000
Daily activities	1.52	0.700	1.20	0.577	0.011
Pain/Discomfort	2.15	0.662	1.26	0.526	0.001
Anxiety/Depression	2.19	0.736	1.26	0.447	0.001

(**) Wilcoxon`s test

pital in Cantabria (Northern Spain), the reference hospital for the Spanish HHT unit, is coordinated by Dr R. Zarrabeitia and supported by Dr L.M Botella from the Biological Research Centre, Madrid (CIB), where genetic studies are carried out and information about the disease compiled. From Sierrallana Hospital, the patients are sent to our ENT unit, for the sclerosing treatment. At this moment, our ENT consultation unit is considered the reference unit in Spain for this treatment.

Most of the patients attending our outpatients' unit, with just a few exceptions, are patients with a long clinical history of the disease who have been subjected to multiple treatments. All of them suffer from epistaxis and have been subjected to multiple packings, transfusions and cauterizations, etc. Therefore, in our clinical exploration, we not only observed the typical telangiectases, but also the complications due to previous treatments such as mucosal atrophy, sinequiae, lack of septal cartilage and even perforations. All of these conditions complicate the manipulation of the nostrils, prone to bleeding due to mucosal fragility

Conclusions
1. Sclerosing infiltrations with Aethoxysklerol® are efficient to control epistaxis in HHT or Rendu-Osler-Weber syndrome.
2. The administration of this technique is not too complex, as it does not require a general anaesthesia under normal conditions.
3. Side effects are minimal, since we have only registered one case of septal perforation from among 300 infiltrations, and another of enlargement of a pre-existing perforation due to the technique.

Conflict of interest statement
The authors declare that they have no conflicts of interest.

Authorship contribution
DM: The main author involved in the evaluation of the sclerosing treatment and in the editing, of the present manuscript. TM: Help in the sclerosing treatment and in the revision of the clinical cases. RZ: Coordinator responsible for sending Rendu-Osler patients from the reference hospital of Sierrallana, Torrelavega (Spain) for local sclerotherapy. LMB: Help in sending patients from the CIB (Madrid) and in editing the English edition of the manuscript. AA: Responsible for the design and statistical treatment of data.

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