Effective prophylaxis of visual and neurological disturbances with an anti-endothelin drug: analysis of 1642 sclerotherapy sessions

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Abstract

In the literature cases of stroke and transient neurological symptoms have been described after sclerotherapy for chronic venous disease

The initial interpretation of these phenomena was that of a micro air embolism in association with a patent foramen ovale. This explanation did not always manage to justify all neurological manifestations. Recent theories have demonstrated that in the area of sclerosis, a significant amount of endothelin 1. We carried out a retrospective assessment of sclerotherapy case studies on 540 patients at ten phlebological centres to search for a relationship between the use of aminaftone (a venotropic drug with demonstrated anti-endothelin action) and the occurrence of side effects after sclerotherapy was performed. Significant reduction of side effects was observed in sclerotherapy for teleangectasias and in patients with migraine history.

Introduction

Sclerotherapy for lower limb varicose veins reticular veins and teleangectasias is a technique that has been used for many years; however, it was only after the introduction of sclerosing foam that its use spread across the world and it now plays an important role in the treatment of chronic venous disease.[1] In addition, recently, national and international guidelines have included ultrasound guided foam sclerotherapy (UGFS) among the available selection of therapies for the treatment of varicose disease. Case studies increasingly report results that substantially overlap with those obtained with methods of thermal ablation or surgery but with a significantly lower impact on QoL and, if performed correctly, sclerotherapy with foam is a safe procedure with low incidence of complications.[2-10]

A recent meta-analysis of the complications of sclerosing foam identified a low incidence of adverse events and thus confirmed the substantial safety of treatment with foam solutions.[11]

However, scotomas or paresthesia occur immediately after 1.4 % of treatments, and in migraineurs the onset of a migraine crisis is not uncommon. Moreover, cases of stroke and transient neurological symptoms have been described and myocardial infarction without ST-segment elevation.[12,13] The appearance of these serious complications, although extremely rare, has led the scientific community to seek a pathogenetic explanation.

The initial interpretation of these phenomena was that of a micro air embolism in patients with a patent foramen ovale (PFO) or another type of left-right shunt; this explanation did not always manage to justify all neurological manifestations. Recent theories have demonstrated that in the area of sclerosis, a significant amount of endothelin 1 (ET-1), our body's most powerful vasoconstrictor, is released.[14] In the literature, the relationship between the presence of high quantities of ET-1 and the cerebral and retinal vasospasm or one of the phases of the migraine crisis is clear.[14] A relationship between the release of endothelin and the onset of myocardial infarction without ST-segment elevation after sclerotherapy has also recently been documented.[13]

In previously published studies, it has been demonstrated that in an animal model of sclerotherapy, a significant increase in systemic ET-1 occurs after sclerosis with polidocanol (POL) or with sodium tetradecyl sulphate (STS) both in liquid form and foam. In addition, in a study carried out in patients subjected to sclerotherapy where systemic endothelin was measured in a vein in the vicinity of the sclerosed vein, we also demonstrated a significant increase in ET-1 both at systemically and locally with a significant relationship between the two values.[15]

Some anti-endothelin drugs such as aminaftone (AMNA) are currently available which, in the absence of significant side effects, have proven to have significant anti-ET-1 properties. In a study published in 2014, we demonstrated that in both the animal model and in the model built on Human Umbilical Vein Endothelial Cells (HUVEC) it was possible to significantly reduce the release of ET-1 after sclerotherapy by performing a pretreatment with aminaftone.[16]

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Aim of the study

Aminaftone is used extensively in clinical practice in Italy and, for this reason, we carried out a retrospective assessment of sclerotherapy case studies at ten phlebological centres to search for a relationship between the use of aminaftone and the occurrence of side effects after sclerotherapy. Due to the retrospective design of the study it was not possible to have homogeneous procedures in the treatment of patients.

Materials and Methods

Aminaphtone is frequently used in the phlebological practice in Italy. We carried out a retrospective assessment of the case study of treatments with sclerotherapy at ten Italian phlebological centres for a period from January 2013 to February 2014. All the doctors involved had substantial experience with sclerotherapy. At the Centres where Aminaphtone (Capillarema Laboratori Baldacci Pisa-Italy) was used, the drug was administered orally at a dose of 150 mg in two daily administrations starting the treatment three to seven days prior to sclerotherapy. The drug used is regularly recorded in Italy as a vein protector and, as the study is retrospective, there was not a true randomization. The sclerosis was carried out according to the routine protocols of each centre and no provision has been issued to change the treatments that were carried out. All the centres involved had a database where the characteristics of the therapy and any adverse events were recorded thus facilitating

data collection. The statistical analysis was performed with the statistical package SPSS version 23 by IBM for MAC.

Two tails Chi square statistics with the conventional significance level of 0.05 was applied for the comparison of the percentages of different outcomes in different subgroups. Yates continuity correction and exact tests were performed were indicated.

Results

1642 sclerotherapy sessions for 540 patients were assessed. In 1212 cases, a concomitant therapy with aminaftone was used, while in 430 cases, sclerosis was not performed with associated AMNA therapy. No other associated therapies with potential anti-endothelin effect have been used.

In patients with no associated aminaftone treatment, the sclerosis was performed with STS in 11.1% of cases while in the remaining 88.8% cases, POL was used. In the group where AMNA was used, 96.7% of cases had been injected with polydocanol and only 2.3% with sodium tetradecyl sulphate. The average concentration of the sclerosing agent was different to the concentration in the STS group where it was 1.78% while in patients treated with POL it was 2.6%. The mean volume of sclerosants was 4.4 ml in the group without prophylaxis and 4.1 in the AMNA group.

The adverse events considered in this analysis were transient visual disturbances (usually scotoma), neurological disorders (typically transient paraesthesias or hyposthenias) and the onset of migraine crises.

Figures 1 and 2 indicate the distribution of veins subjected to sclerotherapy in the two groups.

In the sessions carried out without associated therapy with aminaftone, complications occurred in 1.62% of cases (one of these even after a sclerotherapy with liquid), while in patients undergoing therapy in conjunction with the administration of aminaftone the percentage of complications was 0.57%. In particular, the analysis of just the subset of sessions carried out with aminaftone and a total amount of sclerosing agent less than 5 cc revealed a lower percentage of complications: 0.18% (P=NS).

In the subgroup analysis, it was possible to identify the numerically more significant group in patients treated for telangiectasias, to determine that in the absence of a concomitant treatment with aminaftone the percentage of complications recorded was 2.3% while there were no adverse events among the treated patients (P=0.02).

In other groups for example, in the treatment of recurrences, positive trends were recorded (with AMNA 0% adverse events recorded – without AMNA 4.7% adverse events recorded), but due to the limited number of observations it was not possible to reach statistical significance. In saphenous veins, percentages of complications were 1.08% (AMNA) and 0.95% (no AMNA) (P=NS) respectively, despite the analysis having been carried out in the group where a volume of foam lower than 5 cc was used.

Regarding the migraine crises in patients where the sclerosis was carried out without concomitant treatment with aminaftone, 3% reported a history of headaches, while in the group with aminaftone, as much as 7.6% of the sessions were carried out in a patient with a history of headaches.

In 38.4% of the sessions conducted in the presence of a history of headaches and without concomitant treatment with aminaftone, an adverse event occurred. On the contrary if the patient was taking aminaftone only 3.2% of cases showed a complication (P=0.002).

Discussion

The use of sclerotherapy in the treatment of chronic venous disease has seen a significant increase in recent years.[4] Current guidelines now consider that sclerotherapy, and in particular that with foam, is an adequate therapy in the case of saphenous insufficiency and some consider it more appropriate than surgical treatment.[2,17]

A meta-analysis conducted by Jia revealed the substantial safety of the treatment with minimum percentage of transient complications and a very low incidence of major complications.[11]

In spite of this, it is necessary to understand the mechanism of these complications if we want to make the treatment even safer.

The initial explanation of the onset of transient visual and neurological events was air microembolism. Indeed, the study by Guex[18] revealed that the incidence of these complications increases with the introduction of sclerosing foam in clinical practice. However, the same study shows that these complications are also present, albeit at a lower percentage, in patients being treated with the sclerosing drug in liquid form. Indeed, both visual and neurological complications were reported in the literature concerning sclerosis with liquid.[18-20] In these cases, a cause linked to the presence of air or gas that can cause a paradoxical embolism through a PFO or another type of

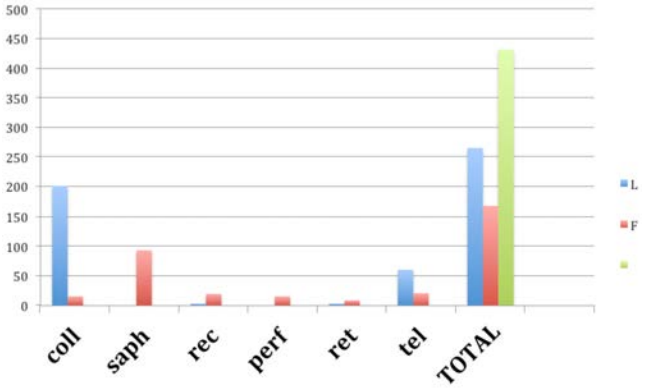

Figure 1. Vein distribution without aminaftone prophylaxis (coll, tributaries; saph, saphens; rec, recurrences; perf, perforators; ret, reticular veins; tel, teleangectasias).

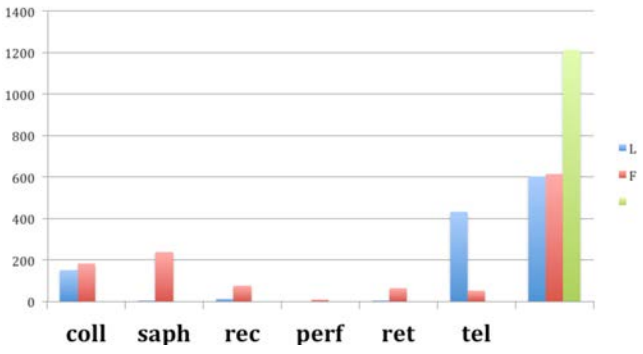

Figure 2. Vein distribution with aminaftone prophylaxis (coll, tributaries; saph, saphens; rec, recurrences; perf, perforators; ret, reticular veins; tel, teleangectasias).

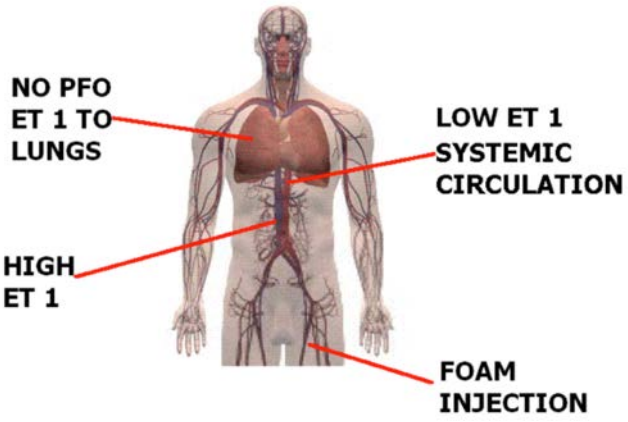

Figure 3. Endothelin 1 (ET-1) circulation without patent foramen ovale (PFO).

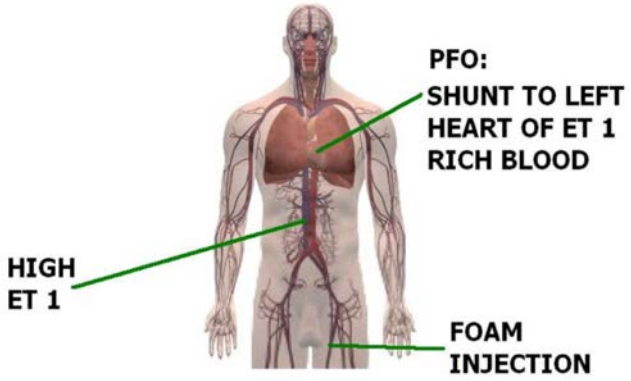

Figure 4. Endothelin 1 (ET-1) circulation in presence of patent foramen ovale (PFO).

shunt cannot be established. It is also surprising that adverse events occur almost exclusively in the cerebral region or in the eye.

A precise relationship between high levels of endothelin 1 and cerebral and retinal vasospasm has been described in the literature. ET-1 is also one of the mediators in the vasoconstrictive phase of migraine.[14-16]

We published a pathogenetic hypothesis to explain these events where we assumed that the sclerosed vein releases ET-1. Generally, endothelin passes through the pulmonary circulation, but in the presence of a PFO a faster flow of blood rich in ET-1 in the left sections of the heart may occur. Indeed, endothelin has a very short half-life and pulmonary vessels are rich in ET-1 receptors.[14] Therefore, in the event of a fast flow of blood rich in ET-1 in the left ventricle, it is easy to understand how vasospastic type complications can occur (Figures 3 and 4).

The actual onset of these complications may be modified by a number of factors:

- increased release of ET-1 from the sclerosed vein, which is greater using large quantities of foam or treating large endothelial surfaces. In addition, the data in the literature also indicates an increased basal release of ET-1 from varicose veins;
- the presence of PFO or other types of shunt with a more rapid passage of endothelin in arterial circulation;
- incomplete venous spasm of the sclerosed segment: the formation of a lumen with an inflamed endothelium and therefore with a persistent flow will allow greater release of ET-1, contrary to a spasmed vessel and therefore without flow;
- variability between patients: the endothelin receptor expression is variable;
- interaction with anti-endothelin substances.

Even if there is not any demonstration of the role of additional mediators in the pathogenesis of complication, the hypothesis of additional substances in this process must be considered.

Conclusions

The role of microbubbles in the development of visual and neurological complications after sclerotherapy is greatly overestimated in the absence of valid proof of a relationship between the presence of air or gas and the symptoms. Moreover, it does not explain the almost total absence of reports of complications in other locations or the onset of these complications with the use of liquid, when air or gas are not clearly present.

This analysis has clear limits because it is not a prospective, randomised study but it provides significant data for the prophylaxis of complications in the treatment of telangiectasias and especially in patients with a history of migraines. Indeed, in the latter, a prophylaxis with a molecule with anti-ET-1 properties like aminaftone has led to a tenfold reduction in the risk of the onset of a transient complication. Furthermore, in this study, there was a clear trend in favour of increased safety by limiting the total volume of 5 cc sclerosing agent per session. In view of these results and the excellent safety profile of the drug, it would be interesting to assess these preliminary results with a prospective study, which we consider highly advisable.

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