POST-SCLEROTHERAPY HYPERPIGMENTATION
(Pathophysiology and therapy)

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Introduction
Post- sclerotherapy hyperpigmentation following the treatment of either varicose veins and/or visible blood vessels (telangiectasias) in the lower limbs has always been a major problem for the phlebologist.

In literature there are conflicting data on the true incidence of this complication. In some studies the incidence is estimated in 30% of patients treated with sodium tetradecyl sulphate and from 10.7% to 30% with polidocanol (lauromacrogol, 400). According to Avramovic (1989) the remaining hyperpigmentation that remains after treatment is by far the most common complication (3.5% of 7200 patients treated), while "the Australian Polidocanol Study" reports an incidence of 0.31% in 8177 lower limbs one year after sclerotherapy with polidocanol (or lauromacrogol, 400). The varying data found in the studies probably depend on the fact that inhomogeneous "end points" such as vessel diameter, the observation times, the sclerosing agents and the technique used, have been considered. The incidence is closely related to operator-dependent causes, such as the choice of concentration and dose of the drug and the injection technique. It is however also related to non-operator dependent factors such as skin type and ferrokinetics (Table 1). The relationship between the risk of hyperpigmentation and sclerotherapy agents have been reported in numerous studies which show a higher frequency of complications with the use of sodium tetradecyl sulphate compared to chrome glycerin. The frequency is also higher after sclerosis of the small vessels, since the more superficial layers of the skin are less vascularized than the dermis.

Pathogenesis
Post-sclerotherapy hyperpigmentations exhibit linear-macular morphology, rarely just dots, with shades from gray to dark brown and usually appear 6-12 weeks after sclerotherapy. The light brown pigmentation that arises shortly after therapy usually disappears within a year.

The pathogenetic hypotheses proposed are numerous:
- Tournay (1966) believed that they were hemosiderin pigmentation with variable melanistic parts;
- Chatard (1976), Orbach (1979) and Wenner (1981) agreed about hemosiderin, secondary to perivenulitis by sclerosing agents and intravascular microthrombosis;
- Shields and Jansen (1982) and Bodian (1985) attributed the haemosiderin deposit to diapedesis of erythrocytes after sclerotherapy.

Some controlled biopsy studies (Barner 1977; Cuttel and Fox 1982; Goldman 1987) finally clarified that the deposit of blood iron in tissues caused the hemosiderin pathogenesis pigmentation. The relationship between melanin and hemosiderin were studied by Ackermann (1988) and by Cheatle (1991) have pointed out that the melanocytic activation is secondary, over a period of years, to the accumulation of ferric pigment in the dermis.
The pathogenetic stages are summarized as follows (Table II):

- Injecting sclerotherapy agents causes erythrocyte diapedesis, either by direct effect of the trauma from the needle or by the alteration of the blood vessel permeability inherent in the mechanism of sclerosing agent action (Fitzpatrick 1959)

- The heme iron released is complexed with the apoferritin protein part to form ferritin, which represents the "mobile pool" of ferric deposit

- The following degradation of ferritin in hemosiderin seems to be conditioned by the environmental pH acid (Izzo, 1993) that results in the loss of the proportion of apoferritin protein and its water solubility (typical of ferritin), while retaining the ability to be solubilized in strong acids.

The relationship between sclerotherapy agents with acid pH-osmolality and the appearance of pigmentation therefore has a pathophysiological justification (Izzo, 1993).

**Therapy**

The numerous therapy proposals can be grouped into "non-drug" and "drug". The results to date have been inconsistent and disappointing, even with the most complex and expensive methods. The main problem is to be able to chelate and/or solubilize the hemosiderin component. For this purpose, we have used two categories of pharmacological agents:

- Chelates: EDTA, desferoxamine;

- Solubilizing hemosiderin solutions: trichloroacetic acid, alpha-hydroxy acids, mercaptoacetic acid (or mercaptoacetic).

The solubilizing haemosiderin solutions are of particular interest since hemosiderin is soluble in strong acids (Izzo, 1993). The hemosiderin accumulates in the dermis (especially in the papillary layer), so acids that have the characteristics to easily overcome the epidermal layer are necessary (derma chemical peeling). We used three recent acids for topical use:

1) Alpha-hydroxy acids: in particular glycolic acid to 70%; they have not shown consistent results because they are not able to quickly and effectively reach the dermis for their surface-exfoliating keratolytic action.

2) Trichloroacetic acid (TCA): very strong acid, soluble in water, alcohol and ether, has a P.M. of 163.4 and has a strong denaturing protein power with excellent and rapid skin penetration and ability to solubilize the hemosiderin deposited in the dermis. In concentrations up to 30% the action is limited to the papillary dermis, while between 30 and 60% it can reach the reticular dermis-hypodermis. For topical use: skin erythema (1-10 minutes), exfoliation or "peeling effect" (5-10 minutes) and coagulation of the proteins ("frost effect or white frost") for longer application times (over 10 minutes). The side effects described are post-inflammatory hypopigmentation and scarring from chemical burns due to the use of an exaggerated concentration, extended contact times or application on unsuitable skin. The studies of Bernier (1989) with TCA in aqueous solution at 10-40% and our most recent (1993) with TCA in amphiphilic solution (fat-soluble) to 10% have shown excellent results. The application is carried out exclusively in the hyperpigmentation area after thorough skin cleansing, the average exposure time is about 2-5 minutes or until you see a slight reddening of the skin, the area is then washed with water, saline or bicarbonate buffer solution. Applications are performed every 5-15 days until the disappearance of the pigmentation. Recently
(Izzo, 1995) also used a kind of modified Kligman triad composed of TCA, 2% hydroquinone and 0.05% retinoic acid with satisfactory results.

3) Mercaptoaetic acid or thioglycolic: is the acid most recently used, and in our opinion, the one that was more effective when applied topically in concentrations of 10-20%. It has the advantage of not burning or producing erythema with a transient and slight exfoliation. Shoden (1960) demonstrated a strong affinity for hemosiderin with its rapid dissolution action. Joo (1990) and Hoffmann (1991) have shown its ability to deplete splenic accumulations of iron in animals, thanks to the presence of thiol groups -SH and an antioxidant activity, as it is one of the main metabolites of carboxymethylcysteine (with mucolytic sebum-regulating and anti-radical) activities. These data have led us to use the mercaptoacetic acid (SIDERLINK) for topical use (10 and 20%) in the therapy of post-sclerotherapy hyperpigmentation, even present after several years, with excellent and rapid results (Izzo, 1995). Its strong haemosiderin activity solubizing the iron in the epidermis level is probably not only due to the acidity of the compound but also to the presence of the thiol group, which gives it a high affinity for iron ion in the skin. This medical device associates both the solubilizing and the complexing iron effect. The affinity of the mercaptoaetic acid to ionized iron is similar to that of apoferritin, and then allows it to bind electively to the hemosiderina, ensuring a good efficacy even at low concentrations, in contrast to other strong acids used. It requires shorter application times, at most a few minutes, and is subsequently removed by washing with water or buffer substances.

Mercaptoaetic acid currently presents a real therapeutic advance in the field of post-sclerotherapy pigmentations for its fast-acting, effective and free of side effects when properly used.

All this must not, however, make us forget that the first duty that every phlebologist must respect is the implementation of the basic rules to reduce the risk of appearance of pigmentation in patients treated with sclerotherapy. These rules are as follows:

- Careful choice regarding sclerotherapy agent, its concentration and dosage in relation to the size and morphology of the vessels to be treated, using correct therapeutic strategy and tactics;
- Suspension of drugs interfering with haemostasis and eventually favoring the bleeding (NSAID, antithrombotic, fibrinolytic etc.);
- Suspension of drugs and potentially pigmentation cosmetics (tetracycline, chloroquine, suntan lotion, dyes, bergamot oil etc.);
- Avoid sunlight or tanning lamps in the immediate post-sclerotherapy period;
- Assessment of ferrocin and individual skin type (table).

BIBLIOGRAPHY


TABLE I

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<th>Operator dependent factors</th>
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<td>1. Vessel state and fragility</td>
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TABLE II

**SCLERO SIDEROSIS**
(Pathogenic stages)

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Sclerotherapy injection
    ↓
Erythrocyte diapedesis
    ↓
Phagocytosis erythrocytes dermal
    ↓
Heme – Iron
    ↓
Tissue ferritin (mobile pool)
    ↓
Hemosiderin (stable pool)
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