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Review Article

Skin hyperpigmentation after sclerotherapy with polidocanol: A systematic review

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Abstract

Skin hyperpigmentation after sclerotherapy with polidocanol-containing sclerosants is a common local side effect. Sclerotherapists should be familiar with factors that trigger hyperpigmentation after sclerotherapy with polidocanol-containing sclerosants.

A systematic literature review of works reporting hyperpigmentation after sclerotherapy for telangiectasias, reticular veins, side branches, and truncal varices with polidocanol-containing sclerosants was performed. Reported incidence rates, follow-up periods, and potentially triggering factors were assessed and analysed. The search yielded 1687 results; of these, 27 reports met the inclusion criteria. The incidence of hyperpigmentation seemed to increase with higher concentrations of polidocanol and was more evident after sclerotherapy for epifascial veins than for intrafascial truncal veins when the polidocanol concentration was more than 0.25%. Regarding sclerotherapy for telangiectasias and reticular veins, the incidence of hyperpigmentation ranged between 2% and 25% for polidocanol 0.25% (liquid and foam), between 12.5% and 67.9% for polidocanol 0.5% (liquid and foam), and between 13% and 73% for polidocanol 1% (liquid and foam). Regarding truncal veins, the incidence ranged from 7% to 45.8% for polidocanol 1% (liquid and foam), from 16% to 17% for polidocanol 2% (foam), and from 7.4% to 32.5% for polidocanol 3% (liquid and foam). Regarding the treatment of side branches, the incidence of hyperpigmentation ranged from 5.6% to 53% for both foam and liquid sclerotherapy. Regarding the duration of hyperpigmentation, there are few data describing reticular veins and telangiectasias. Hyperpigmentation persisting for more than 6 months has been reported to have an incidence of up to 7.5%. Hyperpigmentation persisting for more than 1 year after foam polidocanol 1% to 3% treatment for truncal veins has an incidence ranging from 8.1% to 17.5%.

Other factors such as higher volumes and compression therapy after treatment seem to have a minor influence. Data regarding hyperpigmentation after polidocanol-related sclerotherapy are poor and should be improved by higher-quality research.

Keywords: hyperpigmentation, pigmentation, sclerotherapy, polidocanol, varicose veins, reticular veins, telangiectasia

Introduction

Chronic venous disorders are associated with a wide clinical spectrum ranging from cosmetic problems to severe skin damage including ulceration.[1] In addition to conservative therapies and surgical and endovenous procedures, sclerotherapy is an integral part of treating truncal veins and side branches, as well as smaller cosmetically disturbing telangiectasias and reticular varicosity.[2]

Sclerotherapy comprises targeted injection of a sclerosing agent into the varicose vein or telangiectasia with direct damage to the endothelium by destruction of the intima and fibrosis of the endothelial wall. [2,3] Sclerosants introduced between 1930 and the 1960s and are still widely used include chromated glycerin, sodium tetradecylsulphate, and polidocanol. The introduction of foam sclerotherapy with polidocanol and sodium tetradecylsulphate during the early 1990s further improved and enhanced the effect of sclerotherapy. However, sodium tetradecylsulphate seems to cause significantly more hyperpigmentation and more pain at the injection site. Therefore, polidocanol-containing sclerosants such as Aethoxysklerol® are widely used as standard sclerosants.[3]

Foaming with air or carbon dioxide creates so-called micro air bubbles in micelles. The bubbles comprise a highly concentrated sclerosant on the surface and have an enhanced lytic effect on the endothelial cells of the treated varicosity.[3,4] Because of the foam viscosity, the effect is localised. Therefore, severe systemic and local side effects such as deep vein thrombosis and skin necrosis are rare.[4,5]

In addition to telangiectatic matting, a common local side effect of polidocanol-containing sclerosants is hyperpigmentation of the skin above and around the treated vein. It can persist for months to years, thus causing unsatisfying results and loss of quality of life for patients; furthermore, these patients tend to feel the need to undergo expensive brightening therapies like resurfacing laser techniques.[6,7] Although hyperpigmentation as a side effect is widely known, there is a significant lack of evidence regarding its pathophysiology and triggering factors. Moreover, the term hyperpigmentation is poorly defined in quantitative terms. Furthermore, there is substantial bias in clinical studies because of the lack of standardised protocols for the clinical evaluation of hyperpigmentation.

This review aimed to summarise the currently available literature regarding polidocanol-containing sclerosants in a systematic manner and analyse the incidence rates, follow-up periods, and potentially triggering factors associated with post-treatment hyperpigmentation.

Methods

Literature search strategy

A systematic literature search of PubMed, MeSH, and Google Scholar electronic databases was performed according to the PRISMA guidelines. The search was conducted until December 2021. The database searches were also augmented with electronic and hand searches of journals not consistently indexed in the major databases, such as Phlebologie (Germany) and Phlébologie (France). The search strategy included combinations of the following MeSH terms: "sclerotherapy" AND "hyperpigmentation" AND polidocanol"; "sclerotherapy" AND "pigmentation" AND "polidocanol"; "sclerotherapy" AND "complications" AND "polidocanol"; "varicose veins" AND "sclerotherapy" AND "pigmentation" AND "polidocanol"; and "varicose veins" AND "sclerotherapy" AND "hyperpigmentation" AND "polidocanol". Based on the title and abstract of the publication, works including clinical data regarding side effects of sclerotherapy were pooled and reviewed in detail. All works reporting hyperpigmentation were selected.

Inclusion and exclusion criteria

All publications including hyperpigmentation after leg vein treatments with polidocanol-containing agents alone or in combination with other therapies (other sclerosants, surgery, cutaneous laser) were considered for review. Non-human studies, studies missing the full text, reviews, case reports, works about treatment sites other than the legs, works about sclerosants other than polidocanol, "combination therapies" (e.g., polidocanol with other sclerosants, polidocanol in combination with surgical or other endovenous procedures), works missing information about the concentrations of sclerosants or the incidence of hyperpigmentation, and works in languages other than English, German, and French were not considered.

Data extraction, analysis, and quality assessment

The data of each selected work were assessed and extracted by two independent authors (SB and CD). These data included the following: author; year of publication; study design; number of treated patients; type of varicose veins; type of polidocanol (liquid or foam); concentration and volume of polidocanol; number of therapy sessions; number of reported hyperpigmentation; time of appearance and duration of hyperpigmentation after therapy; compression therapy used; and compression therapy duration. The quality of the included

studies was independently reviewed by three reviewers (SB, CD, and TW) using the GRADE approach.[8] Any disagreements among the reviewers regarding study selection and quality were resolved by consensus (SB, CD, and TW). Articles with the same authorship were excluded to avoid repeated inclusion of the same cohort. Meta-analyses were not performed because of considerable heterogeneity of the selected studies.

Results

A total of 1687 articles were yielded by the search; of these, 27 met our inclusion criteria (Figure 1). There were 15 randomised trials and 12 non-randomised studies (comparative and observational studies). Skin hyperpigmentation after sclerotherapy was observed in all types of varicose veins treated.

Thirteen of the 27 publications (9 randomised controlled trials [RCTs] and 4 non-RCTs) described skin pigmentation after the treatment of telangiectasias and reticular veins. In the remaining 14 publications, hyperpigmentation was reported after the treatment of varicose side branches and truncal veins (6 RCTs and 8 non-RCTs). We divided the search results of the studies according to the type of veins treated: reticular veins (<3 mm) and telangiectasias (<1 mm) (Table 1) and larger veins, such as the great saphenous vein and side branches (>3 mm), and smaller veins (Table 2).

Concentrations, volumes, and physical condition of polidocanol

Telangiectasia and reticular varicose veins

Liquid and foam with concentrations of 0.25% to 1% were used to treat telangiectasias and reticular veins. The evaluation of all RCTs and non-RCTs showed more hyperpigmentation with increasing concentrations: with polidocanol 0.25% (liquid and foam), the range of hyperpigmentation was 2% to 25%[7,9-13]; with polidocanol 0.5% (liquid and foam), the range of hyperpigmentation was 12.5% to 67.9%[7,10,13-18]; and with polidocanol 1% (liquid and foam), the range of hyperpigmentation was 13% to 73%.[7,10,12-14,16,17,19,20]

A comparison of 0.25% polidocanol liquid and 0.25% polidocanol foam showed that the range of hyperpigmentation was comparable: 4.4% to 25% for liquid polidocanol and 2% to 20% for foam polidocanol.[7,9-13] Two studies directly compared the side effects of 0.25% polidocanol liquid and 0.25% polidocanol foam.[9,11] During the RCT by Kern et al., there were no significant differences in hyperpigmentation between groups.[9] A comparative study by Benigni et al.

showed four-times more hyperpigmentation; however, the number of patients (20 patients) was considerably small in this trial.[11]

With 0.5% polidocanol, the rate of hyperpigmentation was lower with liquid sclerosant (12.5%-30%)[7,10,13,14,17,18] than with foam (13%-67.9%).[10,13,15-17] With polidocanol 1%, the rate of post-treatment hyperpigmentation associated with liquid polidocanol[7,10,12-14,17,19,20] was higher than that associated with foam[10,13,16] (14.3%-73% vs. 14.8%-23%). The volumes used were not always mentioned in the publications. The maximum volumes for liquid polidocanol at all concentrations and foam polidocanol were 28 mL and 10 mL, respectively.[7,9-20]

In all studies that included foam sclerotherapy with concentrations of 0.25% to 1% polidocanol (7 studies), the foam was produced using the Tessari method. Two studies involving 0.25% polidocanol used the Monfreux technique.[9,11]

Truncal veins and varicose side branches

The majority of truncal vein treatments involve foam polidocanol with a concentration ranging from 1% to 3%. The hyperpigmentation rates reported by all RCTs and non-RCTs during this analysis (liquid and foam) were 7% to 45.8% for polidocanol 1%,[21-26] 16% to 17% for polidocanol 2%,[27,28] and 7.4% to 32.5% for polidocanol 3%.[21,22,24,25,28-30.]

One randomised study compared polidocanol 3% liquid and polidocanol 3% foam. The authors found slightly less hyperpigmentation in the foam group than in the liquid group (7.4% vs. 9.6%) with almost the same injected volumes (liquid or emulsified foam).[29]

Two RCTs compared polidocanol 1% foam and polidocanol 3% foam. The hyperpigmentation rates ranged from 19% to 22% for polidocanol 1%, and from 18% to 28.2% for polidocanol 3%; again, there were no significant differences in the applied volumes.[21,22]

For side branches, 0.5% to 3% polidocanol was applied as liquid and foam. Most of the studies lacked precise data regarding hyperpigmentation according to the concentrations used. The hyperpigmentation rate ranged from 5.6% to 53% for both foam and liquid sclerotherapy.[31-33]

Only one RCT reported detailed data of hyperpigmentation. Zhang et al. demonstrated that the incidence of hyperpigmentation was associated with increasing concentrations of polidocanol liquid at virtually the same volumes (5.6% for polidocanol 0.5%; 15.7% for polidocanol 1%; and 26.4% for polidocanol 3%, p-value <0.001).[33]

A direct comparison of liquid and foam for the treatment of side branches was performed during one RCT. Polidocanol was applied as liquid and foam with concentrations of 1% to 2.5% for the treatment of reticular veins and side branches. There were significantly more

hyperpigmentation cases in the foam group using higher volumes of polidocanol (2 mL per session, 53%; 0.5 mL per session, 15%, p-value <0.0001).[32]

Most sclerotherapies with 0.5% to 3% polidocanol were performed using the Tessari method for foam production (10 studies). One study used Turbofoam for foam generation,[22] and another used polidocanol endovenous microfoam 1%.[26] Regarding the type of gas used for foam production, one study compared air-based foam and CO_2-based foam and reported significantly less hyperpigmentation in the CO_2 group (p-value <0.0001). Detailed data regarding pigmentation according to the polidocanol concentrations used were not collected.[24]

Time of appearance and duration of hyperpigmentation

During most studies, hyperpigmentation was observed within 1 month at the first follow-up examination (Tables 1 and 2). There were differences in the durations of hyperpigmentation. After sclerotherapy for telangiectasia, the longest follow-up period was only 6 months after the last injection. Therefore, the RCT with the longest observed follow-up period reported a hyperpigmentation rate of 7.5% within 6 months of treatment.[19]

When truncal veins were treated with foam polidocanol with concentrations of 1% to 3%, the rate of hyperpigmentation after more than 1 year ranged from 8.1% to 17.5%, and the rate of hyperpigmentation was higher with polidocanol 2% to 3% than with 1%.[21,27] The study with the longest documented follow-up period reported hyperpigmentation after sclerotherapy rates of 4% (polidocanol 1% foam) and 9% (polidocanol 3% foam) after 3 years.[22]

Compression therapy after sclerotherapy

Compression therapy after sclerotherapy was performed during most of the included studies (Tables 1 and 2). For sclerotherapy of telangiectasia and reticular varices, cotton balls and compression bandages and/or compression stockings (23-32 mmHg) were applied for up to 3 weeks. During the study with the longest period of compression therapy after sclerotherapy with 0.5% polidocanol foam, the hyperpigmentation rate was 67.9% after 6 months.[15] For the treatment of truncal veins and side branches, compression therapy (compression bandages and/or stockings) was performed for 48 hours to 12 months. During the study with the longest period of compression therapy (12 months after treatment) with 2% polidocanol foam of the great saphenous vein, the hyperpigmentation rate was 15%.[27]

Discussion

During this systematic review, we evaluated the available scientific evidence of skin hyperpigmentation after polidocanol-based sclerotherapy for varicose veins. To our knowledge, this is the first systematic review of this topic.

Our research revealed a significant lack of evidence and that the included studies were of limited quality. This was rather surprising because polidocanol-based sclerotherapy has been an established method of treatment for decades, and because hyperpigmentation after treatment is a common and undesired local side effect. Hyperpigmentation leads to an unsatisfied patient and a frustrated physician. Therefore, it would be useful to gather scientific evidence of the pathophysiology and triggering factors of this phenomenon to find a solution.

Until now, one important obstacle to the scientific evaluation of hyperpigmentation has been the lack of an objective measurement tool to score and compare hyperpigmentation. Triggering factors and the effects of treatment interventions can be studied reliably only when an objective hyperpigmentation assessment is available. Recently, a new validated method of scoring hyperpigmentation, the Skin Hyperpigmentation Index, has been suggested and validated by our group and could become a feasible tool for scoring hyperpigmentation, especially in the scientific setting, in the future.[35,36]

Our research has revealed that the incidence of skin hyperpigmentation increases with higher concentrations used for the treatment of small veins, such as spider veins and reticular varices, and for larger veins, such as side branches (Figure 2). Therefore, the highest incidence of hyperpigmentation was found for epifascial veins, such as telangiectasias, reticular veins, and side branches, but not for the truncal veins. This suggests that the intrafascial course of the truncal veins represents a barrier limiting pigmentation toward the outside. Two reasons for this observation could be hypothesised. First, the fascia is a visual barrier; therefore, hemosiderin deposition cannot be detected by the naked eye in that layer. Second, inflammation is limited to deeper layers and does not affect the upper dermis, where the majority of post-inflammatory hyperpigmentation by melanin is produced. In epifascial veins, the brown discoloration of hemosiderin deposition is more visible through the skin and is further complemented by post-inflammatory melanocyte stimulation of the dermis.

Regarding the question of whether foam or liquid polidocanol causes more hyperpigmentation, the results were heterogenous. The type of foam production (Tessari, Monfreux, polidocanol endovenous microfoam, or CO_2-based) does not seem to have a role in hyperpigmentation. During sclerotherapy of smaller veins with 0.25% polidocanol, the incidence of skin pigmentation was comparable with both liquid and foam sclerotherapy. However, the rate of

hyperpigmentation appeared to be greater with foam sclerotherapy involving concentrations of 0.5% or more, especially during the treatment of larger epifascial veins, but not of intrafascial truncal veins. One explanation for the higher incidence occurring with foam sclerotherapy could be the more efficient mechanism of action resulting in higher occlusion rates and stronger inflammatory reactions. The foaming action of polidocanol pushes blood away and makes better contact with the endothelium through the formation of micelles. Therefore, the foam works more efficiently, but it also causes more inflammation, which eventually leads to hemosiderin deposition by extravasated erythrocytes and melanocyte stimulation through inflammation.[35,37] Our results showed that this effect is enhanced not only with increased concentrations but also with increased vein sizes and the epifascial location of the affected vein.

The duration of hyperpigmentation was dependent on the concentration used and the size of the veins treated. According to our results, long-lasting hyperpigmentation after polidocanol foam could be detected in up to 9% of patients after 3 years.[22] In this context, the question of whether compression therapy can reduce post-inflammatory hyperpigmentation after sclerotherapy arises. In terms of efficacy, compression therapy after sclerotherapy has shown some benefits over placebo, but only for telangiectasias.[38] For side branches and truncal veins, there seems to be no advantage in terms of efficacy over placebo, as shown by several studies.[37,39,40] In terms of side effects such as hyperpigmentation, compression therapy showed no significant benefits, although it should be noted that objective quantitative evaluation protocols were lacking, and that often it was only documented whether hyperpigmentation of any degree was present.[37-40] The current European guidelines recommend compression up to 3 weeks after sclerotherapy for telangiectasia, but not for junctional sclerotherapy of truncal veins, which may favourably influence side effects such as hyperpigmentation; however, evidence-based data are lacking.[40] Our data also showed that hyperpigmentation could be detected even if compression therapy was applied for up to 1 year.

Other factors potentially influencing the appearance and course of hyperpigmentation

Studies have shown a linear correlation between increased ferritin levels and pigmentation severity, which is also strongly correlated with refractory hyperpigmentation lasting longer than 12 months.[41]

Some authors have suggested the reduction of iron supplements for up to 1 month after sclerotherapy as well as abstention from bleeding-promoting drugs, such as non-steroidal anti-inflammatory drugs, as other preventive measures to reduce hyperpigmentation.[42,43]

Venoactive drugs, such as sulodexide or micronised purified flavonoid fraction, have resulted in reductions in hyperpigmentation after sclerotherapy when added to sclerotherapy and continued for several weeks.[10,44,45] However, the quality of the evidence regarding this issue is poor.

Microthrombectomy with multiple punctures days to weeks after sclerotherapy resulted in promising outcomes, including reduced hemosiderin deposition and possible reduction of hyperpigmentation.[44,46] However, evacuation of thrombus material usually only partially reduces hyperpigmentation. This is related to the pathomechanism, which has been determined to be a combination of intradermal hemosiderin deposition and dermal melanocyte reaction stimulated by the developing inflammatory reaction. Therefore, sclerotherapy for epifascial veins within the dermis may cause significantly more visible hyperpigmentation. Additional external factors such as friction and ultraviolet exposure that additionally trigger post-inflammatory melanocyte stimulation should be avoided. Individuals with darker pigment may be more susceptible because they are more sensitive to melanocyte stimulation, which is also involved in other post-inflammatory inflammatory dermatoses; however, the contrast may be much more pronounced in fair skin types.[35,47] In addition to the aforementioned factors favouring the development of hyperpigmentation, it seems essential to focus attention on the clean technical performance of sclerotherapy. In this regard, technical factors such as limiting the intravascular pressure during injection as well as first treating locations with high reflux pressure, larger vessels before small vessels, and proximal areas before distal areas may help minimise hyperpigmentation.[41,46,47]

We have summarised the predisposing factors and possible prophylactic measures to prevent hyperpigmentation (Table 3). Nevertheless, most preventive measures are based on experience, and large-scale studies are lacking.. Treatment options of hyperpigmentation are limited to short-pulsed pigment lasers, and triple cream containing hydroquinone, tretinoin, and topical steroids.[47,48] However, scanty data exist regarding the best treatment options due to limitations in number of studies and quality with lack of objective measurement methods.[35,36]

Pretreatment information of the patients

Considering the results and conclusions of our investigation, we strongly recommend that patients should be informed about the advantages and disadvantages before treatment. It is important for patients to be aware of hyperpigmentation so that their expectations of outcomes are reasonable, and so that they can accept this common phenomenon with patience.

Conclusion

We reviewed the available evidence of hyperpigmentation after polidocanol-based sclerotherapy for varicose veins; however, the evidence of this common side effect is scarce. The currently available data indicate that the incidence of skin hyperpigmentation increases with higher polidocanol concentrations in liquid and foam for the treatment of truncal veins, side branches, telangiectasias, and reticular veins. Concentrations of more than 0.5% polidocanol and foam sclerotherapy seem to cause more hyperpigmentation than liquid sclerotherapy, especially for epifascial veins such as side branches, reticular varices, and telangiectasias.

The sclerosant volume, multiple treatment sessions, and compression therapy after treatment did not show any effects on hyperpigmentation. The large incidence range may indicate inconsistencies in the methods of assessing hyperpigmentation and reporting its incidence over time. Studies with better designs, such as large-scale RCTs, involving objective quantification of hyperpigmentation are needed to achieve a better understanding of this frequent complication after this common treatment.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data search, selection, and assessment was performed by SB, CD, and TW. All authors assisted in the interpretation of the data. SB and TW wrote the manuscript. AAR, HU, KH, and SC helped revise the manuscript.

Figure and Table legends

Figure 1: Search strategy according to the PRISMA flow chart.

Figure 2: Incidence of hyperpigmentation with different polidocanol concentrations according to the reviewed literature.

Table 1. Studies from the literature search that treated reticular veins and telangiectasias

Table 2. Studies from the literature search that treated larger veins such as the great saphenous vein and side branches and smaller veins

Table 3. Factors minimising the probability of hyperpigmentation

Table-1

Author, year	Design	Patients, n	Vein type	Sclerosant, concentration, foam/liquid	Foam/liquid volumes	Sessions, n	Hyperpigmentation rates	Time of appearance after therapy	Hyperpigmentation duration	Compression therapy and duration
Norris MJ, 1989	RCT	20	Telangiectasia and reticular veins	POL 0.25, 0.5, 0.75 and 1%, liquid	2 mL	1 to 5	25% (POL 0.25%), 20% (POL 0.5%), 50% (POL 0.75%), 60% (POL 1%)	4-24 weeks	NA	48 h-2 weeks
Weiss RA, 1990	RCT	113	Telangiectasia and reticular veins	POL 1%, liquid	NA	1	30.70%	1 month	>6 months: 7.5% (POL 1%)	No (only cotton balls)
McCoy S, 1999	RCT	81	Telangiectasia and reticular veins	POL 1%, liquid	NA	1	73%	2 months	NA	No
Kern P, 2004	RCT	150	Telangiectasia and reticular veins	POL 0.25% liquid/foam	NA	1	2% (POL 0.25% foam), 4.4% (POL 0.25% liquid)	5 weeks	NA	1 week
Peterson JD, 2012	RCT	63	Telangiectasia and reticular veins	POL 0.5% and 1%, liquid	Average: 1.43 mL POL 0.5% and 1.83 mL POL 1%	1	20.6% (POL 0.5% and 1%)	4 weeks	>3 months (19%)	1 week
Parlar B, 2014	RCT	56	Telangiectasia and reticular veins	POL 0.5%, foam	NA	2	67.90%	6 months	NA	3 weeks
Hoss E, 2020	RCT	30	Telangiectasia and	POL 0.5% and 1%, foam	Maximum: 6 mL	2	23% (POL 0.5% and 1% foam)	3 months	> 3 months	1 week

			reticular veins							
Ochoa AJ, 2021	RCT	720	Telangiectasia and reticular veins	POL, 0.25%, 0.5%, 1%, liquid/foam	Maximum POL: 10 mL foam and 28 mL liquid	2	14.8% (POL 0.25%, 0.5%, and 1% liquid/foam)	1 month	>3 months: 10.4%	1 week
Bayer A, 2021	RCT	50	Telangiectasia and reticular veins	POL 0.5% and 1% liquid and 0.5% foam	NA	1	13% (POL 0.5% and 1% foam/liquid)	4 weeks	NA	Bandages, 24 h; stockings, 1 week
Benigni JP, 1999	Comparative study	20	Telangiectasia and reticular veins	POL 0.25%, foam/liquid	7.25 mL foam and 19.8 mL liquid	5	20% (foam) and 5% (liquid)	3 months	NA	NA
Albanese V, 2002	Comparative study	44	Telangiectasia and reticular veins	POL 0.25% and 1%, liquid	NA	1 to 2	14.3% (PO, 0.25% and 1%, liquid)	6 months	>6 months	3 days
Levy JL, 2004	Comparative study	14	Telangiectasia and reticular veins	POL 0.5%, liquid	NA	1	12.50%	3 months	>3 months	No (cotton-wool balls)
Uncu H, 2010	Comparative study	100	Telangiectasia and reticular veins	POL 0.25%, 0.5%, and 1% liquid/foam	2.5 mL	Mean: 2.5 for foam and 2.7 for liquid	20% (foam) and 30% (liquid)	1 month	NA	Bandages, 48 h; stockings, 8 days

NA, not applicable; POL, polidocanol; RCT, randomised controlled trial

Table-2

Author, year	Design	Patients, n	Vein type	Sclerosant, concentration, foam/liquid	Foam/liquid volumes	Sessions, n	Hyperpigmentation rates	Time of appearance after therapy	Hyperpigmentation duration	Compression therapy and duration
Goldman MP, 2002	RCT	129	Telangiectasias, reticular and varicose veins ,leg veins	POL 0.5%, 1% ,and 3%, liquid	Maximum: 10 mL	1	53% (0.5%, 1%, and 3%, liquid)	4 months	NA	NA
Alos J 2006	RCT	75	Reticular veins and side branches	POL 1% to 2.5% liquid, 0.5% to 1.25% foam	2 mL POL foam, 0.5 mL POL liquid	1	15% (liquid), 53% (foam)	1 month	>1 year: 6.3% (liquid), 33% (foam)	48 h
Ceulen RPM, 2007	RCT	80	GSV	POL 1% and 3%, foam	Foam mean: 5.3 mL for POL 1%, 5.1 mL for POL for 3%	1.2 (mean)	22% (POL 1%), 28.2% (POL 3%)	1 month	>1 year: 8.1% (POL 1%), 17.5% (POL 3%)	6 weeks
Rabe E, 2008	RCT	106	GSV	POL 3% liquid/foam	Foam mean: 3.8 mL; liquid mean: 3.3 mL	1 to 3 (mean)	7.4% (foam), 9.6% (liquid)	3 months	NA	2 weeks
Blaise S, 2010	RCT	143	GSV	POL 1 and 3%, foam	Foam means: 6.1 mL for POL 1%, 6.4 mL for POL 3%	1 to 4	19% (POL 1%), 18% (POL 3%)	6 months	3 years: 4% (POL 1%), 9% (POL 3%)	Bandages, 3 days; stockings, 15 days
Zhang J, 2011	RCT	285	Teleangiectasias and reticular veins, side branches	POL 0.5%, 1%, and 3%, liquid	Means: 1.97 mL POL 0.5%, 2.11 mL POL 1%, 2.21 mL POL 3%	1 to 3	5.6% (POL 0.5%), 15.7% (POL 1%), 26.4% (POL 3%)	3 months	NA	2 to 4 weeks

Reich-Schupke S, 2010	Observational study	76	Side branches	POL 0.5%, foam	Maximum: 2 mL	3.4 ± 2.7	14.50%	6 months	>12 months: 8.2%	3 weeks
Li L, 2011	Observational study	41	GSV and side branches	POL 1%, foam	Average: 14 mL	1	45.80%	9 months	NA	2 weeks
Hesse G, 2012	Observational study	501	GSV, SSV, side branches	POL 0.25% to 4%, air-based foam and 1% to 3%, CO_2-O_2-based foam	Averages: 5.3 mL for air-based and 8.2 mL for CO_2-O_2	1 to 4	23.3% (air foam), 13.6% (CO_2-O_2 foam)	6-14 weeks	NA	Bandages, 1 to 2 days; stockings, 1 to 3 weeks
Kurnicki J, 2016	Observational study	52	GSV	POL 2%, foam	Average: 7 mL	1	17%	1 month	>1 year: 15%	12 months
Baeshko A, 2016	Observational study	326	GSV	POL 1 and 3%, foam	Maximum: 10 mL	4.2 (average)	32.50%	1 month	NA	1 month
Memetoğlu ME, 2020	Observational study	30	SSV	POL 2% and 3%, foam	Foam median: 4.5 mL	1	16%	1 to 6 months	6 months	1 months
Wu ZP, 2021	Observational study	26	SSV	POL 3%, foam	Average volume: 4.56 mL	1	15.40%	6 months	NA	1 month
Kim PS, 2021	Observational study	60	GSV, SSV, AASV	PEM 1%, foam	Average: 9.3-11.2 mL	1	7%	6 months	NA	Bandages, 3 days; stockings, 15 days

AASV, anterior accessory saphenous vein; GSV, great saphenous vein; PEM, polidocanol endovenous microfoam; POL, polidocanol; RCT, randomised controlled trial; SSV, small saphenous vein

Table 3. Factors minimising the probability of hyperpigmentation

Morphological and technical factors	Interventions that may minimise hyperpigmentation
• Use of lower POL concentrations • Sclerotherapy technique • Limitation of intravascular pressure during injection, initial treatment of larger vessels before small vessels, avoidance of extravasal injection • Use of foam POL ≤0.5% for epifascial veins • Location of the treated vein: the deeper the vein, the less likely the post-treatment hyperpigmentation • Low ferritin levels • Fitzpatrick skin type ≤IV	• Microthrombectomy within the first weeks of follow-up • Prevention of local skin friction • Sun protection after treatment • Low iron intake after treatment • Venoactive drugs after treatment • Compression therapy after sclerotherapy for reticular veins and thread veins

POL, polidocanol

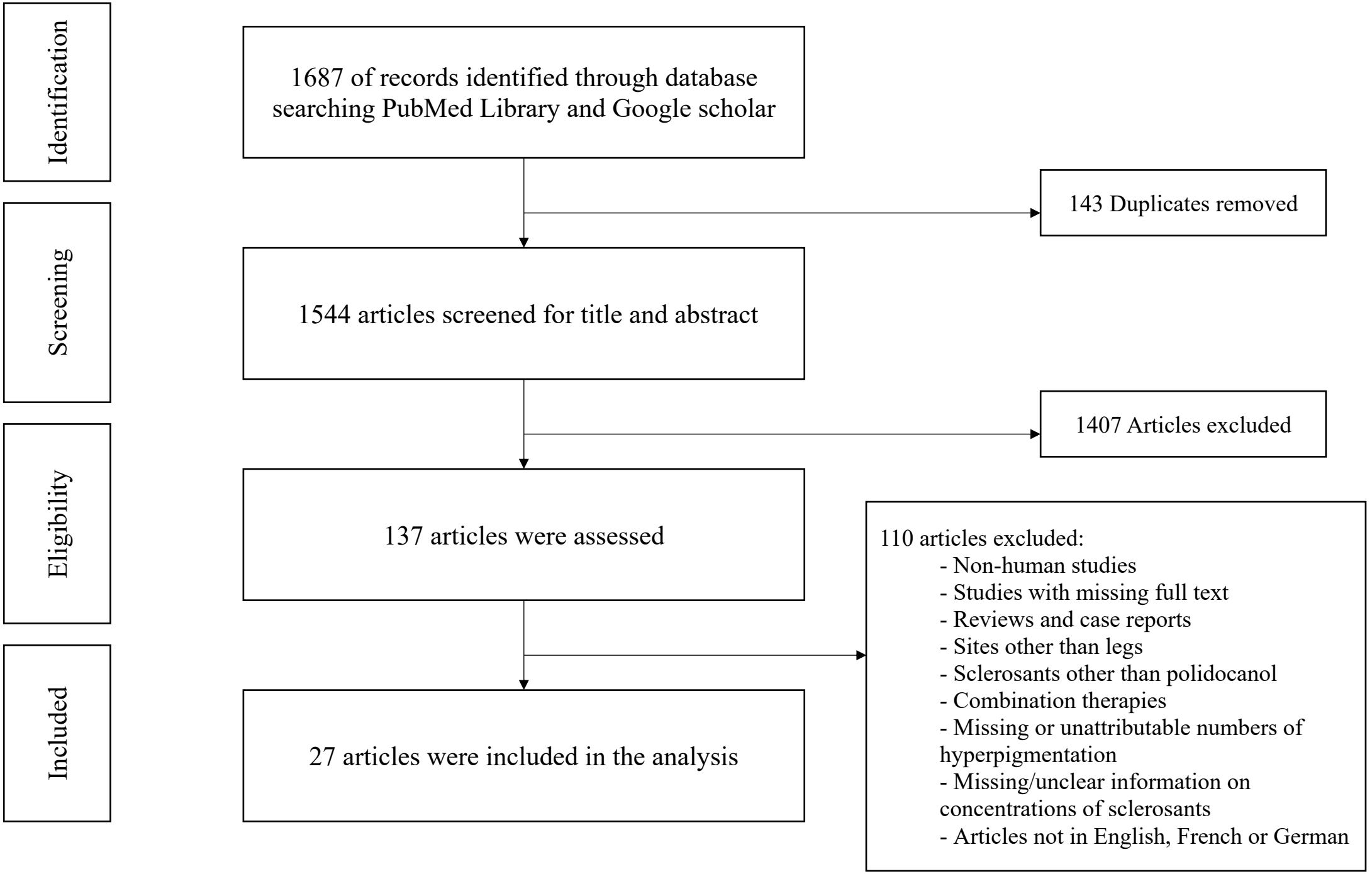
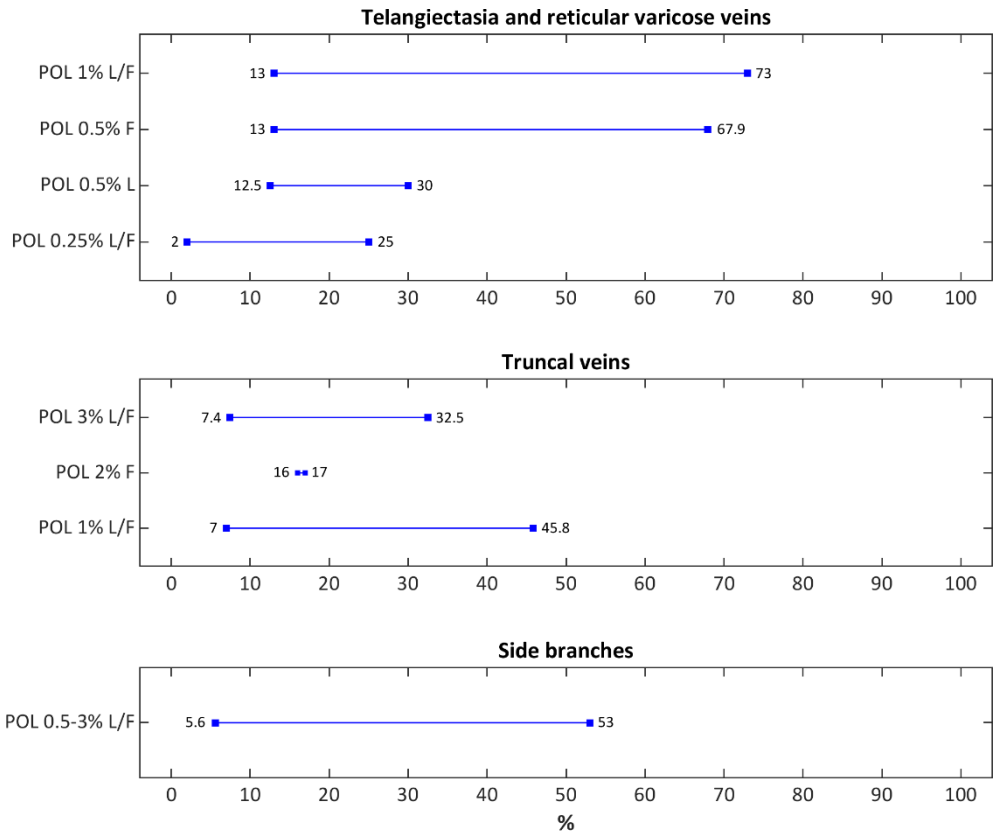

Identification
Screening
Eligibility
Included
1687 of records identified through database searching PubMed Library and Google scholar
143 Duplicates removed
1544 articles screened for title and abstract
1407 Articles excluded
137 articles were assessed
110 articles excluded:
- Non-human studies
- Studies with missing full text
- Reviews and case reports
- Sites other than legs
- Sclerosants other than polidocanol
- Combination therapies
- Missing or unattributable numbers of hyperpigmentation
- Missing/unclear information on concentrations of sclerosants
- Articles not in English, French or German
27 articles were included in the analysis

Figure 2.



L: liquid, F: foam, L/F: no difference whether foam or liquid was used