Double-Blind Prospective Comparative Trial between Foamed and Liquid Polidocanol and Sodium Tetradecyl Sulfate in the Treatment of Varicose and Telangiectatic Leg Veins

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BACKGROUND. Twenty subjects were treated with either polidocanol (POL) or sodium tetradecyl sulfate (STS) to compare the efficacy and adverse sequelae of each agent.

OBJECTIVE. To determine the safety and efficacy of two widely used sclerosing agents.

METHODS. After the exclusion of saphenofemoral junction incompetency, each subject's leg veins were categorized by size (< 1, 1–3, and 3–6 mm in diameter). Each leg was then randomized to be treated with 0.5%, 1%, or 1% foam of POL or 0.25%, 0.5%, or 0.5% foam of STS according to vein size. An independent panel of four physicians, blinded to treatment, performed randomized photographic evaluations obtained pretreatment and 12 weeks post-treatment. Subject satisfaction index and overall clinical improvement assessment were also obtained.

RESULTS. An average 83% improvement was noted for all vein sizes in all subjects with both POL and STS after a single treatment. Subjects were satisfied with treatment, regardless of the sclerosing agent used or the vein size treated. There was no statistically significant difference in adverse effects between each group.

CONCLUSION. Both POL and STS are safe and effective sclerosing agents in the treatment of varicose and telangiectatic leg veins. Both are very tolerable and demonstrate similar post-treatment sequelae.

DR. GOLDMAN RECEIVED THE FIBRO-VEIN AND A STIPEND FOR PERFORMING THIS STUDY.

SCLEROTHERAPY IS a well-tolerated and highly efficacious treatment for varicose and telangiectatic leg veins. Sclerosing solutions act by inducing endothelial damage (endosclerosis), which eventually leads to endofibrosis of the treated vessels. Sclerosing solutions can be placed into three broad categories based on their mechanisms for producing endothelial injury: detergent, osmotic, or chemical irritant solutions. Effective sclerotherapy results when the endothelial damage and associated vascular necrosis are sufficient to destroy the entire vessel wall. The ideal sclerosing solution should be painless to inject, free of adverse effects, and specific for damaged (varicose) veins.[1]

The two most widely used sclerosing solutions worldwide are sodium tetradecyl sulfate (STS) and polidocanol (POL). These detergent-based sclerosing agents have a well-documented history of safety and efficacy spanning 40 to 50 years. This study is the first to compare foamed and liquid Fibro-Vein (a commercial preparation of STS; STD Pharmaceutical Products Ltd., Hereford, England) and Aethoxysklerol (a commercial preparation of POL; Kreussler Pharma, Wiesbaden, Germany) directly with each other in the same patient.

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Materials and Methods

Twenty healthy subjects (19 female, 1 male) with varicose, reticular, and/or telangiectatic leg veins without incompetence at the saphenofemoral or saphenopopliteal junctions were selected to receive sclerotherapy treatment. Each subject's leg veins were evaluated for extent, quality, and size and were placed into one of the following study categories: veins < 1 mm in diameter, veins 1 to 3 mm in diameter, and veins 3 to 6 mm in diameter. Subjects were then randomized to have the veins of either the right leg or the left leg treated with STS and the contralateral leg veins treated with POL. Selection of the concentration and formulation (solution or foam) of sclerosing agent was based on the protocol outlined in Table 1. The treating physician was blinded as to the agent being injected.

Sclerotherapy was performed by standard technique on only one leg in a single treatment session, always by the same physician for a given subject. If foam was necessary,

Table 1. Randomization Protocol

Vein Diameter, mm	*Protocol*
< 1	STS 0.25% solution or POL 0.5% solution
1–3	STS 0.5% solution or POL 1% solution
3–6	STS 0.5% foam or POL 1% foam

POL = polidocanol; STS = sodium tetradecyl sulfate.

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it consisted of 1 mL of sclerosing solution and 4 mL of air, mixed using the double-syringe system technique. Appropriate postprocedure care was conducted, and subjects were asked to keep a record of any adverse events resulting from treatment. All subjects were required to wear class II graduated compression stockings (30–40 mm Hg) around the clock for 7 days following treatment. After having the first leg treated, subjects returned 1 week later for treatment of the contralateral leg. Subjects were seen every 4 weeks thereafter for follow-up.

High-quality digital photographs were taken prior to treatment and at 12 weeks post-treatment. At the end of the study, four independent physicians, who were blinded to the sclerosing agents administered, assessed these images for overall clearance of vessels based on vessel size. Subjects completed questionnaires to assess the tolerability and satisfaction of treatment with each sclerosing agent.

Results

All 20 subjects completed the study (Table 2). For veins < 1 mm in diameter, 19 subjects were treated with STS and 18 with POL. For veins 1 to 3 mm in diameter, 15 subjects received STS and 14 were treated with POL. Ten subjects each were treated with STS and POL in the category of veins 3 to 6 mm in diameter.

STS and POL were found to be equally effective in causing the clearance of veins in all size categories, as per independent, blinded physician evaluations (Table 3). Adverse events were expected and in proportion to the size and extent of treated leg veins. As detailed in Table 4, the incidence of adverse events to treatment was comparable between the two sclerosing agents used, with ecchymosis and hyperpigmentation being the most common. Of note, no skin necrosis was observed in any subject treated with either agent. The results of subject questionnaires are summarized in Table 5. All subjects tolerated STS and POL very well and were pleased with their treatments. Both agents demonstrated equally high subject tolerability and satisfaction (Figures 1 and 2).

Discussion

Sclerotherapy is a popular and effective therapeutic modality for the treatment of varicose and telangiectatic leg veins. The procedure deserves its gold standard label if performed in a logical, stepwise fashion. This article details a clinical study to compare the two most popularly used sclerosing solutions available worldwide. US Food and Drug Administration (FDA) approval is pending for both agents, STS and POL, but they have been used by millions of patients in various forms for more than 50 years, a testament to their safety and efficacy.

Table 2. Subject Vein Characteristics

	Vein Diameter, mm					
	< 1		*1–3*		*3–6*	
Subject	*STS*	*POL*	*STS*	*POL*	*STS*	*POL*
1	X	X	X	X		
2	X	X	X	X	X	X
3	X	X	X	X		
4	X	X	X	X		
5	X	X	X	X	X	
6	X	X	X	X	X	X
7	X	X	X	X	X	X
8	X	X	X	X		
9	X	X	X	X		
10	X	X		X	X	
11	X	X				
12	X	X				
13	X	X	X	X	X	X
14		X	X	X	X	
15	X	X	X	X	X	X
16	X	X	X	X	X	
17	X		X	X		
18	X	X	X	X	X	
19	X	X				
20	X	X	X	X		
Total	19	18	15	14	10	10

POL = polidocanol; STS = sodium tetradecyl sulfate.

Table 3. Clearance Scores at 12 Weeks as Determined by 4 Physician Evaluators*

	Vein Diameter, mm					
	< 1		*1–3*		*3–6*	
Evaluator	*STS*	*POL*	*STS*	*POL*	*STS*	*POL*
1	4	4	4	4	3	3
2	4	4	4	4	4	4
3	5	5	5	4	4	4
4	4	5	5	5	4	4
Average	4.25	4.5	4.5	4.25	3.75	3.75

POL = polidocanol; STS = sodium tetradecyl sulfate.
*Disappearance scoring scale (1–5): 1 = worse than before treatment; 2 = no change; 3 = minimal disappearance (50%); 4 = moderate disappearance (75%); 5 = complete disappearance (100%).

Table 4. Adverse Events by Treatment Group (*N* = 20)

Adverse Event	*STS*	*POL*
Ecchymosis	18	17
Hyperpigmentation	10	9
Coagulum formation	7	8
Local urticaria	5	4
Telangiectatic matting	2	2
Skin necrosis	0	0
Allergic reaction	0	0

POL = polidocanol; STS = sodium tetradecyl sulfate.

Table 5. Average Subject Tolerability and Satisfaction at 12 Weeks Post-Treatment (*N* = 20)

Subject Impression	*STS*	*POL*
Tolerability*	0.40	0.35
Satisfaction†	4.34	4.30

POL = polidocanol; STS = sodium tetradecyl sulfate.
*Tolerability scale (0–3): 0 = no discomfort; 1 = mild discomfort; 2 = moderate discomfort; 3 = severe discomfort.
†Satisfaction scale (1–5): 1 = worse than before treatment; 2 = no change; 3 = minimal disappearance; 4 = moderate disappearance; 5 = complete disappearance.

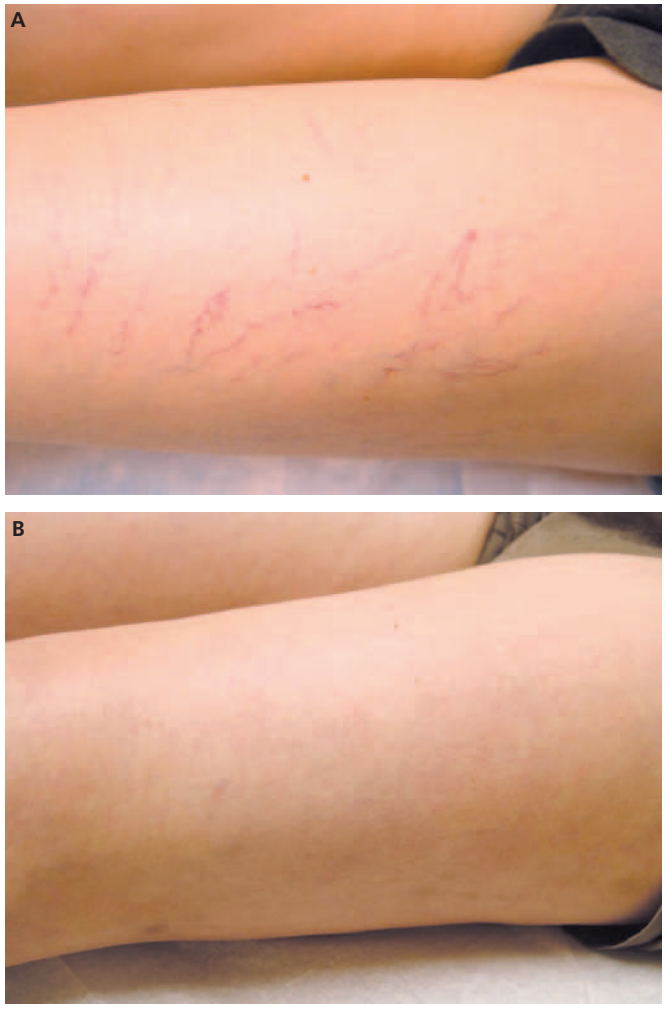

Figure 1. Example of (A) before and (B) 12 weeks post-treatment with Aethoxyskerol.

Sodium Tetradecyl Sulfate

STS is a synthetic, surface-active substance first described by Reiner in 1946.[2] It has been widely used since the 1950s, and many articles have described its safety and efficacy.[1,3–5] It is a long-chain fatty acid salt of an alkali metal with the properties of soap. It is composed of sodium 1-isobutyl-4-ethyloctyl sulfate plus benzoyl alcohol 2% (as an anesthetic agent) and phosphate buffered to pH 7.6. It is a clear solution that is nonviscous, has a low surface tension, and is readily miscible with blood, resulting in a uniform distribution postinjection. The mechanism of action is to disrupt the intracellular cement between the endothelial cells, resulting in desquamation of the cells in plaques. Endothelial destruction results in the exposure of subendothelial collagen fibers. The response to the damage is vein spasm, platelet aggregation, and subsequent fibrosis

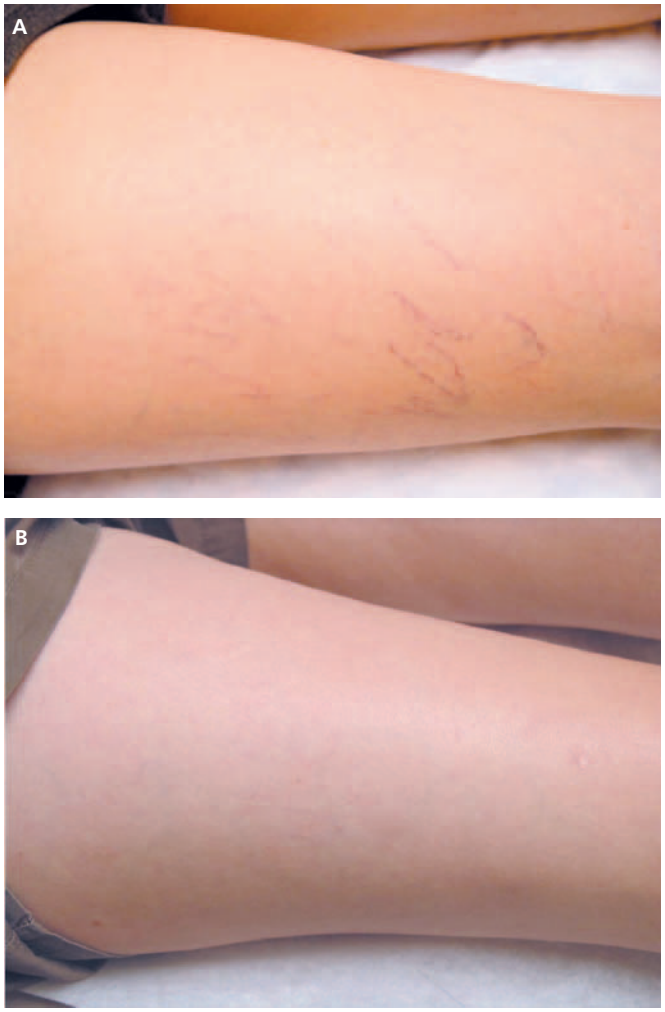

Figure 2. Example of (A) before and (B) 12 weeks post-treatment with Fibro-Vein.

that obliterates the vein. Excess STS is rapidly diluted and neutralized in the bloodstream because it attaches to red blood cells, resulting in hemolysis.

The previously FDA-approved version of STS was manufactured and distributed by Elkins Sinn (a division of Wyeth-Ayerth Philadelphia, PA, USA); however, in 2000, production of this product was discontinued. Since then, there have been no FDA-approved versions of the solution. Currently, the sclerosing agent is being obtained from a variety of other sources, most commonly compounding pharmacies that have been shown to have a variable concentration, pH, and level of contaminants.[6] STS is also available as Trombovein (Omega Pharmaceuticals Ltd., Montreal, Quebec, Canada) and as Fibro-Vein. Fibro-Vein is available in 2 mL ampules in concentrations of 0.5%, 1%, and 3%, as well as 5 mL vials in 0.2% and 3% concentrations.

STS 0.1 to 0.3% in solution form is commonly used for the treatment of telangiectatic leg veins less than 1 mm in diameter; 0.5 to 1% in solution form is useful in treating uncomplicated leg veins 1 to 3 mm in diameter. The use of STS as a foam has expanded its versatility, with 0.25 to 1.0% in foam formulation (created from a 1:4 solution to air ratio) being popular for the treatment of larger reticular and varicose veins (usually 3–6 mm in diameter).[7] Three percent STS foam is popular for the treatment of reflux in the great saphenous vein, with veins of over 10 mm in diameter being treated successfully.[8]

Polidocanol

This is composed of a mixture of hydroxypolyethoxydodecane dissolved in distilled water to which 96% ethyl alcohol is added to a concentration of 5% to ensure emulsification of POL micelles (which provides a clear solution) and to decrease foaming during the production process. The other ingredients are disodium hydrogen orthophosphate dehydrate and potassium dihydrogen orthophosphate.

POL belongs to the class of detergent sclerosing solutions that are nonionic compounds. It consists of an apolar hydrophobic part, dodecyl alcohol, and a polar hydrophilic part, polyethylene-oxide chain, which is esterified. In solution, POL is associated as macromolecules through electrostatic hydrogen bonding between the hydrogen ion of the −OH group in one molecule and the free electron pair of an O_2 dimer of a second molecule. This bonding results in the formation of a network. The sclerotherapeutic activity results from this double hydrophobic and hydrophilic action; thus, POL is a "detergent."

POL is available as Sclerovein (Resinag, Switzerland) in 30 mL multiuse vials in concentrations of 0.5%, 1%, 2%, 3%, and 5%. POL is also available as Aethoxysklerol in 2 mL ampules in concentrations of 0.25%, 0.5%, 1%, 2%, 3%, and 4%, as well as multiuse 30 mL vials in 0.5% and 1% concentrations.

A randomized study determined that a solution of 0.5% concentration might be ideal for sclerosis of telangiectatic leg veins.[9] POL 1% is recommended for veins that are 1 to 2 mm in diameter, POL 2% is recommended for reticular and varicose veins that are 2 to 4 mm in diameter, and POL 3% is recommended for larger veins that are 4 to 8 mm in diameter.[1] The use of POL as a foam has expanded its versatility and increased its use worldwide.

Current Study

This study confirms that STS and POL, in both solution and foam formulations, have similar efficacy, tolerability, and patient satisfaction. There were no notable differences in terms of vessel disappearance or adverse events.

It is worth noting that the results of this study correlate with previous trials comparing these sclerosing agents.[10–12]

However, at the time of those studies, the formulation of STS differed from that currently available. The previously FDA-approved version of the solution manufactured and distributed by Elkins Sinn as Sotradecol is no longer available. A recent analysis of STS obtained from compounding pharmacies indicates the need for a more standardized form of STS.[6] Fibro-Vein is the only pharmaceutically purified version of STS and was the only agent that demonstrated a measured concentration that matched that of the product label (3%). Furthermore, it was noted that Fibro-Vein contained substantially lower amounts of the potentially harmful contaminant carbitol compared with that found in STS produced by compounding pharmacies.[6] It was for these reasons that Fibro-Vein was the formulation of STS used in this study.

Conclusion

This study provides useful data regarding the efficacy, tolerability, and patient satisfaction of two widely used detergent-based sclerosing agents in the treatment of varicose and telangiectatic leg veins. It demonstrates that the standardized, pharmaceutically purified version of STS and POL are equally well tolerated and effective in both solution and foam formulations. STS and POL offer two reasonable and versatile options for the growing practice of sclerotherapy treatment.

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Commentary

This highly informative article, which demonstrates therapeutic parity between different types and formulations of sclerosants, used in equivalent concentrations, reflects a growing consensus among experienced phlebologists.[1] Fortunately for American practitioners, Sotradecol has recently received FDA approval, although the risks of tissue necrosis following the use of higher concentrations of this agent exceed those of polidocanol.[2] Hopefully, at a later date, polidocanol will be approved and used in the United States without medicolegal risks.

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