Title

Treatment of varicose and telangiectatic leg veins: double-blind prospective comparative trial between aethoxyskerol and sotradecol.

Journal

Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 28(1)

ISSN

1076-0512

Author

Goldman, Mitchel P

Publication Date

2002

DOI

10.1046/j.1524-4725.2002.01190.x

Treatment of Varicose and Telangiectatic Leg Veins: Double-Blind Prospective Comparative Trial Between Aethoxyskerol and Sotradecol

Mitchel P. Goldman, MD

Department of Dermatology/Medicine, University of California, San Diego, San Diego, California

BACKGROUND. **One hundred twenty-nine patients 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 sclerosing solutions.**

METHODS. **Each patient's leg veins that did not have incompetence from the saphenofemoral junction (SFJ) were divided into three categories by size (<1 mm, 1–3 mm, 3–6 mm). Each leg was randomly treated with either 0.25%, 0.5%, or 1.5% of STS or 0.5%, 1.0%, or 3% of POL respective of size. An independent, three-panel, blindly randomized photographic examination was obtained pretreatment and at 4 and 16 weeks. Patient satisfaction index and overall clinical improvement assessment were also obtained.**

RESULTS. **All patients had an average of 70% improvement and were 70–72% satisfied in all vein categories treated with either solution. There was no significant difference in adverse effects between each group except for a decrease in ulcerations and swelling in the POL group.**

CONCLUSION. **Both STS and POL are safe and effective sclerosing solutions for varicose and telangiectatic leg veins.**

SCLEROTHERAPY REFERS to the introduction of a foreign substance into the lumen of a vessel causing thrombosis and subsequent fibrosis. The mechanism of action for sclerosing solutions is that of producing endothelial damage (endosclerosis) that ends in endofibrosis. The extent of damage to the blood vessel wall determines the effectiveness of the solution. For sclerotherapy to be effective without recanalization of the thrombotic vessel, the endothelial damage and resulting vascular necrosis must be extensive enough to destroy the entire blood vessel wall.[1] The ideal sclerosing solution should be painless to inject, free of all adverse effects, and specific for damaged (varicose) veins. This article evaluates the safety and efficacy of two detergent sclerosing solutions, sodium tetradecyl sulfate (STS) and polidocanol (POL).

Sodium Tetradecyl Sulfate

Sodium tetradecyl sulfate is a synthetic, surface-active substance first described by Reiner[2] in 1946 (Figure 1). 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 long-chain fatty acid salt of an alkali metal with the properties of soap. The solution is clear, nonviscous, has a low surface tension, and is readily miscible with blood, leading to a uniform distribution after injection.[2] It primarily acts on the endothelium of the vein because, when diluted with blood, the molecules attach to the surface of red blood cells, causing hemolysis. The recommended maximal dosage suggested by the British manufacturer in a treatment session is 4 ml of a 3% solution [S.T.D. injection product data sheet (1977), S.T.D. Pharmaceuticals Products Ltd., Hereford, England]. The recommended maximum dosage by U.S. and Canadian manufacturers is 10 ml of a 3% solution with intervals between treatments of 5–7 days [Tromboject product information (rev. 10/87) from Omega, Montreal, Canada].

It is available as a 1% or 3% solution that can be diluted with sterile water or normal saline to achieve an appropriate therapeutic concentration. It is also available with the same pH and preservative as Fibro-Vein (STD Pharmaceutical Products Ltd., Hereford, England) in 5 ml multiuse vials as 0.2%, 0.5%, 1%, and 3%. Concentrations of 0.1–0.3% are commonly used for the treatment of telangiectatic veins 0.2–1.0 mm in diameter; 0.5–1% for treatment of uncomplicated varicose veins 2–4 mm in diameter; and 1.5–3% for the treatment of larger varicose veins.

STS became widely used in the 1950s after its introduction in 1946 and many articles have been written describing its safety and efficacy.[3–6]

M.P. Goldman, MD has indicated no significant interest with commercial supporters.

Address correspondence and reprint requests to: Mitchel P. Goldman, MD, Dermatology/Cosmetic Laser Associates of San Diego, Inc., 850 Prospect St., La Jolla, CA 92037, or e-mail: MGDERM@aol.com.

ISSN: 1076-0512/02/$15.00/0 • Dermatol Surg 2002;28:52–55

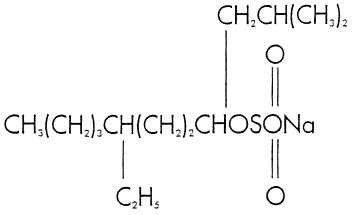

Figure 1. Chemical formula of sodium tetradecyl sulfate.

Polidocanol

Polidocanol (POL) 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. It is available 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. The other ingredients are disodium hydrogen orthophosphate dihydrate and potassium dihydrogen orthophosphate.

The maximum recommended daily dose is shown in Table 1. The LD_{50} in rabbits at 2 hours is 0.2 g/kg, which is three to six times greater than the LD_{50} for novocaine.[7] The LD_{50} in mice has been found to vary between 1.2 g/kg[8] and 110 mg/kg (Kreussler Pharma, personal communication, 1992).

In humans the elimination half-life is 4 hours, with 89% of the dose eliminated from the blood within 12 hours. Amounts excreted in the urine and feces are equal, and almost 80% of the injected compound is excreted via respiration through a breakdown into low molecular weight products. POL is completely eliminated from body organs whether the patient receives one dose or repeated doses. Therefore no accumulation takes place. Polidocanol also does not cross the blood-brain barrier.[9]

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 (Figure 2). In solution, POL is associated as macromolecules through electrostatic hydrogen bonding between the H_2 atom of the OH_2 group in one molecule, and the free electron pair of an O_2 atom of a second molecule. This bonding results in the formation of a network. The sclerotherapeutic activity results from this double hydrophobic and hydrophilic action, and thus POL is a "detergent."

Telangiectases are treated with concentrations of 0.25–0.75%. A randomized study determined that a 0.5% concentration may be ideal for sclerosis of leg telangiectasia.[10] Varicose veins are treated with concentrations of 1–4%. POL 3% is recommended for varicose veins that are 4–8 mm in diameter, POL 2% is recommended for varicose veins that are 2–4 mm in diameter, and POL 1% is recommended for veins that are 1–2 mm in diameter.[6]

An open clinical trial comparing STS with POL was conducted by 120 physicians in Australia. The results at 2 years[11] showed 55 of 65 physicians found that POL had a better efficacy than STS, with 2 claiming decreased efficacy, and 8 seeing no difference. When compared to hypertonic saline (HS), 49 of 58 claimed better efficacy, with 1 physician reporting decreased efficacy, and 8 physicians finding no difference. Pain of injection with POL was less than STS in the experiences of 54 of 65 physicians, with pain being less than HS as reported by 56 of 58 physicians. Finally, the physicians' perceptions of complications were that POL had fewer overall complications (pigmentation, ulceration, phlebitis, telangiectatic matting) according to 58 of 65 physicians as compared with STS, and according to 43 of 58 physicians as compared with HS.

Table 1. Maximal Daily Dose of Polidocanol by Patient Weight

Concentration of POL (%)	*Dose (ml) according to body weight of patient*				
	50 kg	*60 kg*	*70 kg*	*80 kg*	*90 kg*
0.5	20	24	28	32	36
1.0	10	12	14	16	18
2.0	5	6	7	8	9
3.0	3.3	4	4.6	5.3	6

Recommendation of Chemische Fabrik Kreussler & Co GmbH, Wiesbaden-Biebrich D-6202, Postfach 9105, Germany.

Methods

A total of 129 patients with varicose, reticular, and/or telangiectatic leg veins without incompetence at the saphenofemoral or saphenopopleteal junctions were randomized to receive sclerotherapy treatment: 42 with veins less than 1 mm in diameter, 41 with veins 1–3 mm in diameter, and 46 with veins 3–6 mm in diameter were randomized to be treated with either POL or STS. Treatment was performed in a standard technique as previously described.[6] The concentration was chosen based on clinical and experimental experience previously reported.[6,9–12] The treating physician was blinded

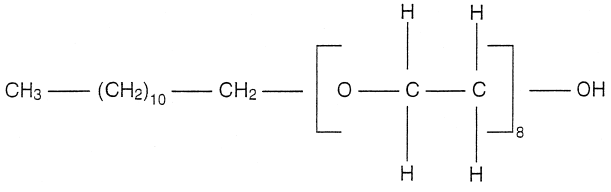

Figure 2. Chemical formula of polidocanol.

Table 2. Disappearance of Varicosities[a]

Vein <1 mm		*Vein 1–3 mm*		*Vein 3–6 mm*		*All*	
STS (N = 32)	*POL (N =26)*	*STS (N = 28)*	*POL (N = 27)*	*STS (N = 27)*	*POL (N = 27)*	*STS (N = 69)*	*POL (N = 60)*
4.4 ± 0.6	4.6 ± 0.4	4.6 ± 0.8	4.4 ± 0.6	4.5 ± 0.4	4.7 ± 0.4	4.5 ± 0.7	4.5 ± 0.5
P = .055		*P* = .832		*P* = .581		*P* = .117	

Disappearance scale (1–5): 1 = worse than before treatment, 2 = no change, 3 = minor disappearance, 4 = moderate disappearance, 5 = complete disappearance.
P = treatment with STS compared to POL; two-way ANOVA.

as to the agent being injected. Veins less than 1 mm in diameter were randomized to be treated with either POL 0.5% or STS 0.25%, veins 1–3 mm in diameter with POL 1% or STS 0.5%, and veins 3–6 mm in diameter to POL 3% or STS 1.5%.

Photographs were taken and questionnaires were administered before treatment and at 1, 4, and 16 weeks after treatment. Three vascular surgeons blinded to treatment and study center evaluated pre- and posttreatment photographs to determine overall disappearance on a scale of 1–5: 1 = worse than before treatment, 2 = no change, 3 = minor disappearance, 4 = moderate disappearance, 5 = complete disappearance.

Results

An analysis of the individual study center and/or treating physician was not performed in this study. To do so would have limited the statistical significance required to properly compare the two sclerosing solutions in the three sizes of veins.

POL and STS were equally effective in causing the disappearance of veins in all size categories (Table 2). Pain, inflammation, hyperpigmentation, ecchymosis, and vein thrombosis were similar with both agents. However, POL caused less localized urticaria and skin necrosis than STS (Table 3).

Discussion

Sclerotherapy is a popular and effective treatment for varicose and telangiectatic leg veins when treatment is performed in a logical stepwise fashion. This article details the largest comparative clinical study to date on the two most popularly used sclerosing solutions available worldwide. STS has been used in the United States and worldwide since the 1950s. It has never been formally investigated under an FDA-required protocol, but its use in millions of patients yearly for the past 50 years attests to its safety and efficacy. POL, another detergent class of sclerosing solutions has been used worldwide since the mid 1960s. It is also used extensively, with millions of treatments being given each year in a safe and effective manner.

We believe that this study as well as the Australian clinical trial[11] and many studies from around the world[6,8,10,13–18] prove that POL is at least as safe and effective as STS for the treatment of varicose and telangiectatic leg veins.

Table 3. Summary of Adverse Events by Treatment Group

Adverse event	*STS*	*POL*	*Total*
Ecchymosis	64 (70%)	48 (58%)	112 (64%)
Hyperpigmentation	58 (64%)	44 (53%)	102 (59%)
Vein thrombosis	42 (46%)	35 (42%)	77 (44%)
Local urticaria	33 (36%)	19 (23%)	52 (30%)
Telangiectatic matting	10 (11%)	6 (7%)	16 (9.2%)
Skin necrosis	6 (6.6%)	0 (0%)	6 (3.5%)
Allergic reaction	0 (0%)	1 (1%)	1 (0.6%)

Acknowledgment The author acknowledges the participation of J. Leonel Villavincencio, MD, Department of Surgery, U.S. University of Health Sciences, Bethesda, MD, for coordinating statistical analysis and Anton Butie, MD, for treating 59 of the 129 patients, and the expert work of John E. Hutton, MD, Christopher G. Cunningham, MD, John D. Martin, MD, and David L Gillespie, MD in reviewing and scoring the photographs. We are indebted to UlrikeTrostmann for her dedicated monitoring work. Partial funding for this study was sponsored by an educational grant from Kreussler & Co. GmbH, Wiesbaden, Germany, and Beiesdorf-Jobst, Inc., Charlotte, NC.

References

1. Hanschell HM. Treatment of varicose veins. Br Med J 1947;2:630.
2. Reiner L. The activity of anionic surface active compounds in producing vascular obliteration. Proc Soc Exp Biol Med 1946;62:49.
3. Nabatoff RA. Recent trends in the diagnosis and treatment of varicose veins. Surg Gynecol Obstet 1950;90:521.
4. Tretbar LL. Spider angiomata: treatment with sclerosant injections. J Kansas Med Soc 1978;79:198.
5. Shields JL, Jansen GT. Therapy for superficial telangiectasias of the lower extremities. J Dermatol Surg Oncol 1982;8:857.
6. Goldman MP, Bergan JJ. Sclerotherapy Treatment of Varicose and Telangiectatic Leg Veins, 3rd ed. St. Louis: Mosby, 2001.
7. Siems KJ, Soehring K. Die Ausschaltug sensibler nerven duren peridurale und paravertebrale injection von alkylpolyathylenoxydathern bei meerschweinchen. Arzneimittelforsche 1952;2:109.
8. Puisseguar Lupo ML. Sclerotherapy: review of results and complications in 200 patients. J Dermatol Surg Oncol 1989;2:214–9.
9. Olesch B. Neuere Erkenntisse zur Pharmakokinetik von Polidocanol (Aethoxysklerol). Arzneimittelforsche 1952;2:109.

10. Carlin MC, Ratz JL. Treatment of telangiectasia: comparison of sclerosing agents. J Dermatol Surg Oncol 1987;13:1181.
11. Conrad P, Malouf GM, Stacy MC. The Australian polidocanol (aethoxysklerol) study: results at two years. Dermatol Surg 1995; 21:334–6.
12. Goldman MP, Kaplan RP, Oki LN, et al. Sclerosing agents in the treatment of telangiectasia: comparison of the clinical and histologic effects of intravascular polidocanol, sodium tetradecyl sulfate and hypertonic saline in the dorsal rabbit ear vein model. Arch Dermatol 1987;123:1196–201.
13. Jaquier JJ, Loretan RM. Clinical trials of a new sclerosing agent: aethoxysklerol. Soc Franc Phlebol 1969;22:393–5.
14. Hofer AE. Aethoxysklerol (Kreussler) in the sclerosing treatment of varices. Minerva Cardioangiol 1972;20:601–4.
15. Amblard P. Our experience with aethoxysklerol. Phlebologie 1977; 30:212–5.
16. Goldman PM. Polidocanol (Aethoxysklerol) for sclerotherapy of superficial venules and telangiectasias. J Dermatol Surg Oncol 1987;13:1181–4.
17. Duffy DM. Small vessel sclerotherapy: an overview. Adv Dermatol 1988;3:221–42.
18. Norris MJ, Carlin RC, Ratz JL. Treatment of essential telangiectasia. Effects of increasing concentrations of polidocanol. J Am Acad Dermatol 1989;20:643–9.