

FDA-Approved Sodium Tetradecyl Sulfate (STS) versus Compounded STS for Venous Sclerotherapy

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BACKGROUND In the area of endovenous chemical ablation (sclerotherapy), there has been much debate regarding sclerosant quality and efficacy. Only sodium tetradecyl sulfate (STS) has garnered Food and Drug Administration (FDA) approval in the United States.

OBJECTIVE The primary objective of this study was to compare clinical performance measures of compounded STS from 27% industrial-strength stock (compounded STS) versus FDA-approved Sotradecol (Bioniche Pharma USA, Inc., Belleville, Ontario, Canada).

MATERIALS AND METHODS Phase I of this study focused on the chemical composition of the drugs, whereas Phase II studied the ablative abilities of the two drugs at comparable concentrations of 3%.

RESULTS We documented the presence of various impurities in compounded STS. No impurities in AngioDynamics STS were found. Our studies suggest that compounded STS may have significant variation in concentration. The AngioDynamics STS concentration was found to be manufactured within a tight tolerance. Segments of incomplete ablation were more frequent in the compounded STS group when compared to the AngioDynamics STS group. This reached statistical significance ($p = .02$). Primary closure using the Kaplan-Meier statistic demonstrated a trend in the favor of AngioDynamics STS when compared to compounded STS.

CONCLUSION When product quality, efficacy, and liability are carefully considered, we conclude that it would behoove physicians to use pharmaceutical-grade, FDA-approved sclerosant when treating their patients.

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Endoluminal destruction of venous tissue is the goal of contemporary venous surgery for the control of axial incompetence of the saphenous vein. This concept can be extended to the great and small saphenous veins, as well as any incompetent accessory or circumflex veins. In addition, varicose venous tributaries and telangiectasias can be treated with endoluminal therapy. Endoluminal delivery of heat or chemicals has become the standard of care and has replaced traditional surgical extirpative techniques.¹

In the area of chemical ablation (sclerotherapy), there has been much debate regarding efficacy, most often discussions include foam versus liquid and the correct sclerosing agent concentration for various techniques.²⁻⁴ Despite this focus, there is little in-

formation available to physicians regarding the issue of sclerosant quality.^{5,6} Although polidocanol and Sotradecol are the two most commonly used agents in modern venous practices, only Sotradecol has garnered Food and Drug Administration (FDA) approval in the United States.

Background

Sodium tetradecyl sulfate (STS) was originally approved by the FDA for manufacture by Elkins Sinn in 1946. Under the Elkins Sinn trade name Sotradecol, STS became the preferred agent for sclerotherapy. When Elkins Sinn discontinued the production of Sotradecol in 2000, a nationwide shortage ensued. Since no other manufacturer had FDA approval to make STS, compounding pharmacies were the only source from which physicians could obtain this agent.

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The shortage of STS and the stopgap role of compounding pharmacies ended in November 2004, when the FDA granted approval to Bioniche Pharma USA, Inc. (Belleville, Ontario, Canada), to manufacture STS in 1 and 3% strengths. Today, FDA-approved Sotradecol is manufactured by Bioniche Pharma in an FDA-approved facility and sold exclusively by AngioDynamics, Inc. (Queensbury, NY).

Physician and Compounding Pharmacy Liability

Distributing and using a compounded drug when an FDA-approved drug is available could create liability exposures for both the compounding pharmacy and the physician who uses the compounded drug. Moreover, if a patient alleging an STS-related injury were to bring an action against a physician who had used a compounded drug rather than the FDA-approved drug, one could easily envision the plaintiff's counsel displaying cost savings by the physician in a highly unflattering light to the jury.

Methods

The primary objective of this study was to compare clinical performance measures of compounded Sotradecol from 27% industrial-strength stock (compounded STS) versus FDA-approved Sotradecol from AngioDynamics, Inc. (AngioDynamics STS). The study was divided into two phases. Phase I of this study focused on the chemical composition of the drugs, whereas Phase II studied the ablative abilities of the two drugs at comparable concentrations of 3%.

Informed consent was obtained from all subjects. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki.

Phase I

Phase Ia evaluated for the presence of impurities in the quality control laboratory at Bioniche Pharma using gas chromatography. Samples of 3% com-

pounded STS and 3% AngioDynamics STS were analyzed. The manufacturer of the compounded STS was The Compounder (Aurora, IL; Batch 081605–130941, expiration August 2006). Phase Ib involved two 30-mL samples of compounded STS from two compounding pharmacies licensed in the United States (The Compounding Shop, St. Petersburg, FL; and The Apothecary Shops, Scottsdale, AZ). These samples were sent to an independent laboratory in the United Kingdom and analyzed using an auto-titrator assay and a manual titration.

Phase II

Phase II involved a clinical study conducted on patients with incompetent great saphenous veins (GSV) treated with 3% STS delivered in a foamed state via an endovenous catheter with proximal balloon control. We limited this study to the GSV because it is considered the sentinel superficial lower extremity vein and the most investigated in the literature. Further, literature regarding GSV ablation with STS foam is inconclusive. During a 16-month period, which extended from January 2005 through April 2006, a total of 51 veins were treated in 37 subjects with catheter-directed sclerotherapy in the Miami Vein Center using a standardized protocol. Men and women were included; the eligible age range was >21 to <76 years. All subjects demonstrated clinically significant reflux of the index vein in the standing position by duplex ultrasound examination. All treated patients were in Class 2 using the CEAP evaluation scale.

The protocol included ultrasound assessment of the GSV with the subject in the supine position. Only GSVs between 4 and 19 mm in diameter were selected for treatment. The treatment length was measured by a tape at the skin level with ultrasound guidance. Vein diameter measurements were made in the transverse view using duplex ultrasound at 4-cm increments from the superficial epigastric vein to the distal introducer access site. The diameter for this cylindrical model was the average of the proximal and distal diameters. The vein volume was

determined by adding the volume of each 4-cm segment throughout the entire treatment length.

The sclerosant was foamed via the Tessari method and delivered with a balloon-controlled endovenous catheter. The Tessari method employs two 10-mL syringes and a standard Luer-lock three-way stopcock. Standard air occupies one syringe and STS the other. The ratio is 4 parts air to 1 part STS. Foam is produced by rapidly mixing the air and STS by alternating injection between the STS syringe and the air-filled syringe. For saphenous closure, a balloon-controlled catheter was used to isolate foam over the desired treatment length and allow contact time to be controlled by the operator.⁷ A 4-minute dwell time was used to insure interaction between the foam and the vein wall. GSV ablation was performed with 3% STS in all cases. In Group 1 ($n = 35$), STS was obtained from a licensed compounding pharmacy (The Compounding Shop). Group 2 ($n = 16$) veins were treated with FDA-approved Sotradecol from AngioDynamics, Inc.

Follow-up ultrasonography of the treatment length per protocol was performed at 2 days, 1 week, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months. The ultrasound examination at each visit was comprehensive. First, subjects were evaluated for the presence of thrombus in the deep venous system of the treated limb. Second, with subjects standing the target superficial vein was imaged throughout the entire treatment length. The treatment

length extended from just distal to the superficial epigastric vein to the site of catheter induction.

The images were reviewed to determine if segments of incomplete ablation (SIA) were present. This was defined as segments within the treatment length that demonstrated venous flow or vein wall compression. Next, the saphenofemoral stump was measured as the distance from the saphenofemoral junction to the proximal closure site in the GSV. Recanalization within the treatment length was defined as any open segment > 5 cm in length.

The percentage of recanalized veins during follow-up and primary closure was calculated by the Kaplan-Meier survival method.⁸ The log-rank test was used to determine statistical difference for primary closure. The unpaired two-tailed *t*-test was used to determine statistical differences between mean age, gender, SIA, and saphenofemoral stump extension. The saphenofemoral stump is defined as the proximal patent length of GSV after therapy.

Results

Sclerosant Purity

Gas chromatography was used to measure impurities in samples of compounded STS and AngioDynamics STS. The results of these studies are summarized in Table 1.

TABLE 1. Phase Ia: Sclerosant Purity

<i>Impurity</i>	<i>Compounded STS</i>	<i>AngioDynamics STS</i>
7-Ethyl-2-methyl-undec-3/4 ene Isomer1	0.64%	Not detected
7-Ethyl-2-methyl-undec-3/4 ene Isomer2	0.07%	Not detected
Benzaldehyde	Not detected	Not detected
7-Ethyl-2-methyl-undec-3/4 ene Isomer3	0.29%	Not detected
Tetradecanol	0.17%	Not detected
Total known	1.17%	Not detected
Carbitol	0.27%	Not detected
Total unknown	0.05%	Not detected
Total impurities	1.49%	Not detected

Compounded STS and AngioDynamics STS are both clear, colorless solutions. In the case of the compounded STS, however, insoluble matter in the form of small white clumps were identified and a number of impurities detected. Impurities were not detected in AngioDynamics STS.

Of particular interest was the presence of carbitol in compounded STS. Carbitol, a solvent used to clean resins and pastes, has the same toxicity as ethylene glycol and is reported to be teratogenic in rats and mice. Carbitol can produce dermatitis and hypersensitivity in humans; the mean lethal dose is 3 to 4 oz.

Sclerosant Concentration

Two 30-mL samples of 3% compounded STS were obtained from separate licensed compounding pharmacies in the United States and sent to an independent laboratory in the United Kingdom for analysis. The results of this analysis are given in Table 2.

For a 3% sample the typical acceptable concentration range is 2.85 to 3.15%. In the case of Batch 123-1 the concentration results fell significantly outside the acceptable range. For Batch 123-2, the carbitol level was 2%, an order of magnitude above the FDA impurity guideline for this drug.

In the course of this study, the Miami Vein Center contacted a licensed compounding pharmacy in Florida from which the center purchased STS for the clinical trial in Phase II. During the course of that trial, the center used seven different lots of compounded STS from this laboratory. We wanted to review the concentration used in our subjects as a function of lot number. We were surprised to find

that this pharmacy does not keep lot samples for retrospective analysis. Further, we learned that the pharmacy does not test for STS concentration as the compounding is performed strictly by weight allotment.

Clinical Results

Over a 16-month period that began in January 2005, two groups of patients underwent GSV chemical ablation at the Miami Vein Center. The first group consisted of 35 veins in 24 patients treated with 3% compounded STS. The second group consisted of 16 veins in 13 patients treated with 3% AngioDynamics STS. The compounded STS group has been followed for a mean of 330 days; the AngioDynamics STS group has been followed for a mean of 137 days. The results of this clinical study are summarized in Table 3 and Figure 1.

Mean age and percent female sex between the two groups were compared and found to have no statistical difference with *p* values of .49 and .22, respectively.

Perfusion of sclerosant for this study was conducted under a standardized protocol using a specific catheter. Our results are based on single injection/session treatment. The duration of injection with this catheter system was in the range of 5 seconds for all injections. The mean sclerosant volume used in the compounded STS group was 9.7 mL (range, 2–20 mL). This compares to 5.2 mL (range, 2–13 mL) in the AngioDynamics STS group. Although the AngioDynamics STS group required less sclerosant, variation in vein geometry reduces the validity of direct comparisons.

Complications were limited to the development of deep venous thrombosis (DVT). In the compounded STS group, one DVT was identified at 1 week in one limb of a duplicated femoral vein. These thrombi resolved rapidly with warfarin therapy. In the AngioDynamics STS group, one DVT was identified at 1 month in a small duplicated femoral vein. The

TABLE 2. Phase Ib: Sclerosant Concentration (Compounded STS)

<i>Batch</i>	<i>STS potency (%)</i>	<i>Carbitol (%)</i>
123-1	2.4	0.00
123-2	3.1	2.00

TABLE 3. Phase II: Results of Clinical Study

Parameter	Compounded STS	AngioDynamics STS	p Value	Notes
Number of veins	35	16	NA	NA
Number of subjects	24	13	NA	NA
Mean age (years)	49.4	47.2	.49	NS, unpaired <i>t</i> -test, two-tailed
% female sex	88.6	75.0	.22	NS, unpaired <i>t</i> -test, two-tailed
SIA (%)	45.7	12.5	.02	Significant, unpaired <i>t</i> -test, two-tailed
Stump extension (%)	71.4	62.5	.38	NS, unpaired <i>t</i> -test, two-tailed
Amount (cm)	0.90	0.64		
Range (cm)	0.00–3.32	0.00–3.00		
Open veins (%)	14.3	12.5	NA	NA
Primary closure (%) (Kaplan-Meier)	91 @ 330 days	100 @ 137 days	.99	NS, log rank test
Mean follow-up	330 days	137 days		

STS, sodium tetradecyl sulfate; SIA, segments of incomplete ablation; NA, not applicable; NS, not significant.

patient was treated with ASA and had no adverse sequelae. This study was clearly not powered to identify differences in DVT.

SIA are believed to correlate with increased long-term recanalization. In the compounded STS group, 45.7% of veins demonstrated SIA some time during follow-up. In the AngioDynamics STS group, this occurred only in 12.5% of veins. This difference was statistically significant with a *p* value of .02.

Saphenofemoral stump extension (increased length of the proximal patent segment of the GSV after therapy) is also believed to correlate with increased long-term recanalization. In the compounded STS

group 71.4% of veins demonstrated stump extension some time during follow-up. In the AngioDynamics STS group this occurred in 62.5% of veins. Although the trend was in the favor of the AngioDynamics STS, the difference did not reach statistical significance with a *p* value of .38.

When primary closure during follow-up was compared, 14.3% of veins recanalized in the compound STS group and 12.5% in the AngioDynamics STS group. Using the Kaplan-Meier statistic and comparing primary closure rate at the mean follow-up point for each, primary closure for the compound STS group was 91 and 100% for the AngioDynamics STS group. Although the trend favors AngioDynamics STS, the difference using the log-rank test did not reach statistical significance with a *p* value of .99. The Kaplan-Meier statistic remains valid if the follow-up period is different for the two groups of interest (330 vs. 137 days). Further, the data are valid for small and different numbers of followed subjects (35 vs. 16). These variables, however, affect the ability of the statistic to determine statistical difference.

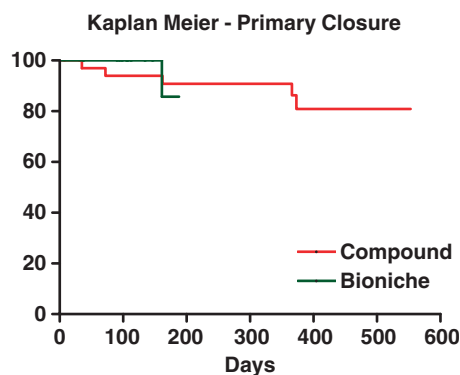


Figure 1. Comparison of primary closure using the Kaplan-Meier statistic.

Discussion

The function of sclerosing agents is to injure the endothelium and, to a minor extent, the media of

the vein wall. The most important qualities that a sclerosant should possess are safety, efficacy, and lack of untoward effects. Other important features should be the ability to produce durable and repeatable results, painless treatments, accurate placement with ultrasound imaging, ease of availability, and low costs. This transfers into highly satisfied patients, which then translates into lessened liability for the treating physician.

Phase Ia of our study addressed issues of STS purity. Although the number of samples we analyzed was limited, the results were clear and certainly raised concerns (Table 1). Compounded STS was found to contain measured levels of impurities, of which the most important was carbitol. Analysis of AngioDynamics STS revealed no measurable level of impurities. Although we cannot document the level of STS impurity necessary to precipitate a clinical event, impurities in other drugs have been linked to significant unexpected adverse events.

The efficacy of sclerosing agents is a function of concentration and vein diameter.² If the target vein diameter is greater than 3 mm, liquid sclerosants lose potency secondary to dilution. As demonstrated from Phase Ib of the study and depicted in Table 2, concentrations of different compounded STS formulations showed significant variation when measured by an independent laboratory. In one sample, the concentration was 20% below the desired 3% concentration level.

In AngioDynamics STS samples, the concentrations were within 1% variability. Compounders could not provide information on the lot numbers of compounded products used in our office, explaining that record keeping was not part of their usual and customary business. Additionally, concentrations were determined by weighing and mixing ingredients, not by potency testing. Thus, we were unable to track the products we were injecting into patients. Should an adverse event such as cutaneous ulceration arise, which has been shown to be partly dependent on the

concentration of the injected sclerosant, this liability would fall on the treating physician.

Sclerosant in the form of foam has clearly improved the results of sclerotherapy. Foam is more efficacious than liquid^{5,6} and is more readily delivered with ultrasound imaging. These are the reasons that it was used in this study. Foam will expand and fill a vein less than 12 mm diameter, offering better contact with the vein wall. Cabrera and colleagues⁹ published a clinical series of 500 lower limbs treated by foam sclerotherapy and reported that after 3 or more years, 81% of treated great saphenous trunks remained occluded and 97% of superficial varices had disappeared. This required one session of sclerotherapy in 86% of patients, two in 11%, and three sessions in 3% of patients.

It is an option for controlling saphenous reflux in veins less than 12 mm and has been shown to be a viable treatment for sclerosis of perforators.¹⁰ Foam is of value in the treatment of varicosed tributaries, tortuous vessels, and venous malformations. Foam also has limitations, however, and carries with it some liability concerns. In veins larger than 12 mm, the sclerosant–blood interface compromises treatment.¹¹ It has been recommended that a 10-mL limit be placed with regard to total foam volume injected because of possible paradoxical embolization via patent foramen ovale.¹² For this reason there has been some interest in maximizing sclerosant contact time with the vein wall through the use of catheters. Future studies will likely focus maximizing results of *liquid* sclerosants through innovations in catheter technology. Therefore, it will be critical to work with standardized formulations of sclerosant for future studies.

Regarding the ablative abilities of compounded STS versus AngioDynamics STS presented as Phase II of the study, we believed that SIA served as a good surrogate for distinguishing qualitative differences between the two drugs. During follow-up, complete duplex ultrasound imaging of the treatment length was performed checking for areas of noncompressibility by gray scale

imaging and segments of perfusion by color-flow duplex imaging. The end point of successful venous ablation is a noncompressible, nonperfused vein which shrinks into a fibrotic cord over time. Unsuccessful venous ablation is characterized by recanalization along the treatment length. Recanalization is usually preceded by the presence of SIA in our experience. We saw a statistically significant difference between AngioDynamics STS and compounded STS with the number of SIA present after treatment.

In this study of 51 treated GSVs with limited follow-up (mean, 330 days for compounded STS and 137 days for AngioDynamics STS), we did not demonstrate on a statistical basis that SIA correlates with vein recanalization. Saphenofemoral stump extension and primary closure rates demonstrated trends that favored AngioDynamics STS over compounded STS.

We documented the presence of various impurities in compounded STS. No impurities in AngioDynamics STS were found. Although we cannot document the level of impurities necessary to trigger an adverse event, impurities in other drugs are known to produce negative clinical outcomes.

Our studies suggest that compounded STS may have significant variation in concentration. AngioDynamics STS concentration was found to be manufactured within a tight tolerance. Concentration may play a role in clinical outcomes.

In the case of a licensed Florida compounding pharmacy, we found that it was not possible to track the origin of the compounded STS used in our patients. Further, we were told no concentration testing was performed and lot samples are not kept for retrospective testing.

SIA were more frequent in the compounded STS group when compared to the AngioDynamics STS group. This reached statistical significance.

Saphenofemoral stump extension was more frequent in the compounded STS group when compared to the AngioDynamics STS group. This was a trend only because no statistical difference could be demonstrated.

Primary closure using the Kaplan-Meier statistic demonstrated a trend in the favor of AngioDynamics STS when compared to compounded STS.

Our work led the investigators to the conclusion that quality assurance programs currently in place at compounding pharmacies are clearly limited. Impurities are present in their products, and stated concentrations may be inaccurate. When product quality, efficacy, and liability are carefully considered, we are left with the conclusion that it would behoove physicians to use pharmaceutical-grade, FDA-approved sclerosant when treating their patients.

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COMMENTARY

When reading this very informative article (obviously with my French eyes), my primary thinking was that we (European phlebologists) are very lucky to have at our disposal sclerosing agents of premium pharmaceutical grade provided by serious (and seriously nationally and EU-controlled) manufacturers.

This is indeed the main conclusion of this study: not all sclerosing agents are the same, and the difference matters much. If a product can be prepared and distributed with care, at verified concentration, and without impurities, why are not all sclerosing agents the same? Not much is known about these impurities; medically speaking that means that they should not be present.

The improvement of the quality of the sclerosing agents we use in France (polidocanol, Kreussler; sodium tetradecyl sulfate, Innothéra; chromated glycerin, Bailleul) is the probable reason for the decrease in the incidence of side effects in my own experience during the past 12 years.^{1,2}

This article also raises interesting concepts about injection procedures (catheter) and assessment of results (segments of incomplete ablation, saphenofemoral stump extension), which deserve further studies, but also plead for the use of pharmaceutical-grade STS.

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