



Effectiveness of foam sclerotherapy on predicting outcomes using ultrasound scoring.

Prédictivité de l'efficacité de la sclérothérapie à la mousse en fonction d'un score de sclérose échographique veineux.

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Summary

Objective: To test the effect of a single injection of different sodium tetradecyl sulfate (STS) dosages on ultrasound scoring system to predict outcomes following ultrasound foam sclerotherapy (UFS) of great saphenous veins (GSVs).

Material and Methods: Sixty-four sclerosed proximal GSVs in 42 patients with saphenofemoral junction incompetence were classified into four groups (A, B, C, D). Images of ultrasound (US) and color flow Doppler (CFD) were retrospectively analyzed with an ultrasonic vein sclerosis scoring system. The vein score was composed of vein wall thickness, lumen filling percentage and vein diameter reduction. Each group received a single injection of STS foam at mid-thigh. Group A was injected with STS 1% 4 mL. Group B with 1% 8 mL, Group C with 3% 4 mL and Group D with 3% 8 mL. The GSVs were analyzed at 1 month and 1 year post-injection.

Statistical methodology: Two way ANOVA analyses, Levene's test, Tukey post hoc test and Games-Howell post hoc test were selected as statistical tools to study the effect of the several dosage treatments and the scoring time on the considered variables.

Results: The overall ultrasonic score was significantly affected by the STS dosage ($P = 0.003$). Using Tukey post hoc test showed that group A had significantly lower overall score compared with group B ($P < 0.05$). There was no significant difference in the ultrasonic score between any other groups ($P > 0.05$). Time of scoring had also significant effect on the overall ultrasonic score with the score being significantly higher at one year compared with at one month (except for group D). There was also significant interaction between dosage and time of scoring indicating that the difference between the four groups did not stay the same over time (comparing one month with one year scores).

Résumé

Objectif: Tester l'efficacité d'une seule injection de tétradécyl sulfate de sodium (STS) à différents dosages en fonction d'un score de sclérose échographique pour prévoir les résultats de la sclérothérapie à la mousse (Ultrasound Foam Sclerotherapy, UFS) de la grande veine saphène (GSV).

Matériel et méthodes: Une série de 64 scléroses proximales de la GSV chez 42 patients ayant une incontinence de la jonction saphénofémorale ont été classifiées dans quatre groupes de sévérité (A, B, C, D). Les images de flux Doppler couleur (CFD) ont été rétrospectivement analysées pour obtenir un score de sclérose échographique de la veine traitée. Ce score est composé par : l'épaisseur de la paroi de la veine, le pourcentage de remplissage de la lumière et la réduction du diamètre de veine. Chaque groupe a reçu une seule injection de mousse de STS au tiers moyen de la cuisse. Le groupe A avec STS 1% 4 mL, le groupe B avec STS 1% 8 mL, le groupe C avec STS 3% 4 mL et le groupe D avec STS 3% 8 mL. La GSV a été analysée en post-injection à 1 mois et à 1 an.

Méthodologie statistique : Deux analyses de variance ANOVA ont été réalisées : le test de Levene, le test post-hoc de Tukey et le test post-hoc de Games-Howell ont été les outils statistiques choisis pour étudier les relations entre les différents dosages thérapeutiques et le score de sclérose échographique.

Résultats : Le score de sclérose échographique global a été significativement affecté par le dosage de STS ($P = 0,003$). L'usage du post-hoc test de Tukey a montré que le groupe A avait significativement un plus faible score sclérose échographique global par rapport au groupe B ($P < 0,05$). Il n'y avait pas de différence significative du score entre tous les autres groupes ($P > 0,05$). Le moment du scoring avait également un impact significatif sur le score de sclérose échographique global : le score était significativement plus élevé à un an par rapport à celui calculé à un mois (sauf pour le groupe D). Il y avait également une interaction significative entre le dosage de la mousse et le moment du scoring ce qui indique que la différence entre les quatre groupes n'est pas restée la même au fil du temps (en comparant le score à un mois avec un score à une année).

Conclusion: The ultrasonic score is significantly affected by STS dosage, time of scoring and interaction between the two factors. Ultrasonic great saphenous vein sclerosis images can be differentiated by their characteristic features of wall thickness, endoluminal filling and vein diameter reduction. The ultrasound vein sclerosis score is useful in prediction of vein successful sclerosis.

Conclusion : Le score de sclérose échographique global est significativement affecté par le dosage de STS, par le moment du scoring et par l'interaction entre les deux facteurs. Les images de sclérose échographique de la grande veine saphène peuvent se différencier en fonction des caractéristiques d'épaisseur de paroi, de remplissage endoluminal et de réduction de diamètre de la veine. Le score de sclérose échographique veineux est utile dans la prédiction du succès de la sclérose de la veine traitée.

Introduction

Varicose veins of the lower extremities is a common condition affecting approximately 25 million American adults [1].

While ultrasound-guided sclerotherapy has been shown to be a highly effective and convenient means of eliminating varicose veins, the origin of the venous incompetence must be identified and treated to reduce the risk of recurrence.

Frequently, the saphenofemoral junction (SFJ) is involved in the varicose vein process [2].

Once identified as the origin, the SFJ can be treated by endovenous chemical or thermal ablation or via surgery.

Veins treated by chemical means with sclerosant develop phlebo-sclerotic changes that naturally mature to form what is considered vein sclerosis. Once treated, the vein is assessed to determine the level of sclerosis that has taken place.

The gold standard diagnostic technique used for detecting vein sclerosis is gray scale ultrasound imaging and color Doppler [2, 3, 4, 5].

Vein compression, visualized via ultrasound and color Doppler, is routinely used to determine the degree of vein sclerosis.

However, the elasticity of vein walls not only vary from patient-to-patient, but vary within individual venous segments and do not remain constant over the time course of sclerosis for all veins. The elasticity of the vein walls is inversely proportional to collagen content; as collagen increases within the vein wall over time, elasticity decreases. Therefore, vein compression as a means of evaluating post-treatment sclerosis cannot be standardized. A means of assessing post-treatment sclerosis that can be standardized across patients (e.g., regardless of age and vein location) and sclerosants is needed to more accurately evaluating sclerosis success. To this end, we developed an ultrasound sclerosis scoring system (USSS) based on vein wall thickness, lumen filling percentage sclerosis, and vein diameter reduction, which are distinct, accurate parameters for sclerosis assessment, using ultrasound and color Doppler images.

The purpose of this study was to conduct a retrospective analysis of patient ultrasound images by scoring the phlebo-reactions of each and determines the effectiveness of various dosages of sodium tetradecyl sulfate (STS) administered as a single injection and augment the prediction of outcomes following endovenous foam sclerotherapy using ultrasound scoring system.

While indications for which sclerosant agent to use to achieve a successful sclerosis is contingent on varicose veins condition, STS, an anionic surfactant, was used in this study because it has been proven to be safe and effective in the treatment of varicosities. STS has been reported to be more effective in its foam formula. However, specific dosage to be effective to induce successful vein sclerosis in proximal great saphenous vein (GSV) incompetence has not been determined.

Therefore, we analyzed four dosages of STS and scored their phlebo-reactions in order to determine the effectiveness of a single injection of STS on predicting outcomes following endovenous foam sclerotherapy (EFS) using this newly developed ultrasound scoring system.

Material and Methods

Patients and Protocol

In this retrospective study, 64 injected proximal GSVs in 42 consecutive qualified patients were studied. The 1-month and 1-year stored grey-scale ultrasound and color flow Doppler images were analyzed retrospectively with an ultrasonic vein sclerosis scoring system.

Inclusion criteria included SFJ incompetence with reflux > 0.05 sec in the terminal or pre-terminal valve without tributaries or perforating veins incompetence above the knee. Injected GSVs were separated into four groups with 16 GSVs in each group (A, B, C, D). The GSVs in these groups were consecutively injected with the following dosages of STS with an air to STS ratio of 4:1 (e.g., 4 mL air to 1 mL STS) prepared using the so-called Raymond-Martimbeau technique [6]:

- Group A: 4 mL of 1% STS foam
- Group B: 8 mL of 1% STS foam
- Group C: 4 mL of 3% STS foam
- Group D: 8 mL of 3% STS foam

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A single injection has been performed at mid-thigh with direct injection technique into the GSV at the saphenous compartment with the patient in supine position. Each patient underwent ultrasound imaging and CFD in erect and supine positions 1 month following injection. Separate scans were also carried out at 1 year. Post-injection maneuvers were the same: immobility for 10 minutes and compression knee-hi hose 30-40 mmHg for 2 weeks for daytime only and ambulation.

Ultrasound Imaging

We used a MyLab™ 25 ultrasound equipment (Esoate) with 7.5-12.0 MHz linear array transducer with the gain set at 70% and a 5 MHz CFD to capture ultrasound data in transverse view.

Vein wall thickness was delineated and measured; lumen filling was delineated and evaluated in transverse plan by vein compression (VC) to deform the GSV; and the percentage of filling was recorded and vein diameter reduction was compared to baseline and estimated in percentage. The scans of the region of interest (ROI) extended along the vein 4 mm proximally and distally and had an error of gradient of ± 4 mm.

Both longitudinal and transverse plans of GSV were interrogated in CFD mode to ensure accurate percentage blood flow.

Scoring System

Each image was evaluated separately for the presence of vein wall thickening, the percentage of lumen filling, and the percentage of vein diameter reduction. If vein wall thickening was present, the image was assigned an ultrasound sclerosis score (USS) of 1; if no thickening was present, the assigned USS was zero. The percentage of lumen filling was calculated and scored based on the following scale:

- 100% = 4 points
- 75% - 100% = 3 points
- 50% - 75% = 2 points
- 25% - 50% = 1 point
- 0% - 25% = 0 point

The percentage of vein diameter reduction was calculated and scored using the same scale as for lumen filling. The USS for each parameter was added for a total score for each image.

Statistical Methodology

In the current paper, two-way ANOVA analyses were selected as the key statistical tool to study the effect of the several dosage treatments and the scoring time on the four considered variables, i.e., ultrasound vein sclerosis scores, vein wall thickness, lumen filling percentage and vein diameter reduction. The two-way ANOVA was considered robust instead of the use of non-parametric approach [7], because the number of subjects per group was constant and the variances were approximately equal. Moreover, the follow-up tests considered the case of violation of the hypothesis of homogeneity of variances. The Levene's test was used to determine if the variances were not equal, and the Tukey post hoc test was selected for the case of homogeneity of variance, whereas the Games-Howell post hoc test was selected if the assumption of equal variances was violated.

Results

Demographics

The demographics of the 42 patients included in the four analyzed groups are presented in **Table 1**. In these patients, GSV incompetence occurred at the pre-terminal valve in 75% of images and at the terminal valve in 25% of images; however, images were not categorized by location of incompetence.

Scores

At 1 month, the mean scores were higher for the two groups that received the higher dosages of STS (i.e., Group B and Group D) than the groups that received the lower dosages of STS. At 1 year, the mean scores were higher than at 1 month for each group except for Group D, for which the mean score decreased slightly.

Table 2 shows the means and standard deviations for the ultrasound vein sclerosis scores separately for the four dosage treatments and time of scoring groups, i.e., month versus year.

Table 3 shows that there was a significant interaction between dosage treatments and time of scoring on ultrasound vein sclerosis scores ($p = 0.000$).

Group	Females	Males	Mean Age (Years)	Pre-injection Mean Vein Diameter (mm)
A	15	1	52.6	6.8
B	16	0	49.4	6.4
C	15	1	51.3	6.9
D	15	1	48.7	6.3

TABLE 1 : Demographics of the Four Analyzed Groups.

Group	Dosage Treatment	Month			Year			Total	
		n	Mean	SD	N	Mean	SD	Mean	SD
A	4 mL 1% STS	16	4.63	0.96	16	7.06	0.93	5.84	1.55
B	8 mL 1% STS	16	6.13	1.20	16	7.63	1.20	6.88	1.41
C	4 mL 3% STS	16	5.94	1.12	16	6.94	1.12	6.44	1.22
D	8 mL 3% STS	16	6.44	1.03	16	6.25	1.06	6.34	1.04
	Total	64	5.78	1.27	64	6.97	1.17	6.38	1.35

TABLE 2 : Descriptive Statistics for Score as a Function of Dosage Treatment and Time of Scoring.
n = number of patients per subset (group); SD = standard deviation.

Variable and Source	Df	MS	F	η^2	p value
Ultrasound Vein Sclerosis Score					
Dosage Treatment	3	5.73	4.88	0.109	< 0.01
Time	1	45.13	38.40	0.242	< 0.001
Dosage Treatment* Time	3	9.56	8.14	0.169	< 0.001
Error	120	1.18			

TABLE 3 : ANOVA for Ultrasound Vein Sclerosis Score as a Function of Dosage Treatment and Time of Scoring.
** $p < 0.01$. Df = degrees of freedom; MS = mean score; F = distribution; η^2 = Eta squared.*

Group	Dosage Treatment	Month			Year			Total	
		n	Mean	SD	n	Mean	SD	Mean	SD
A	4 mL 1% STS	16	0.56	0.51	16	0.75	0.45	0.66	0.48
B	8 mL 1% STS	16	0.81	0.40	16	0.75	0.45	0.78	0.42
C	4 mL 3% STS	16	0.81	0.40	16	0.75	0.45	0.78	0.42
D	8 mL 3% STS	16	0.88	0.34	16	0.44	0.51	0.66	0.48
	Total	64	0.77	0.43	64	0.67	0.47	0.72	0.45

TABLE 4 : Descriptive Statistics for Vein Wall Thickness as a Function of Dosage Treatment and Time of Scoring.
n = number of patients per subset (group); SD = standard deviation.

Eta for the interaction was approximately 0.41, which can be considered a large effect [8].

There was also a significant main effect of dosage treatments on ultrasound vein sclerosis scores, $F(3,120) = 4.88$, $p < 0.01$. Eta for dosage treatments was approximately 0.33, which, according to Cohen (1988), is a medium effect [8]. Furthermore, there was a significant main effect of scoring time on ultrasound vein sclerosis scores, $F(1,120) = 38.40$, $p < 0.001$. Eta for scoring time was approximately 0.49, indicating a large effect.

Levene's test for homogeneity of variance showed that the ultrasound vein sclerosis scores' variances can be assumed to be equal ($p = 0.96$); therefore, post hoc Tukey HSD tests were used and indicated that Group A had significantly lower overall score compared with Group B ($p < 0.01$). There was no significant difference in the ultrasonic score between any other groups ($p > 0.05$).

Vein Wall Thickness

Table 4 shows the means and standard deviations for the vein wall thickness separately for the four dosage treatments and time of scoring groups, i.e., 1 month versus 1 year.

Table 5 shows that there was a significant interaction between dosage treatments and time of scoring on vein wall thickness ($p = 0.048$). Eta for the interaction was approximately 0.41 which can be considered a medium effect.8 However, no significant main effects of dosage treatments or scoring time on vein wall thickness were found, $F(3,120) = 0.85$, $p > 0.05$; $F(1,120) = 1.44$, $p > 0.05$. The Levene's test of equality of variances for the vein wall thickness was significant ($p = 0.004$) indicating that the variances were significantly different. So, the Games-Howell test was selected instead of Tukey in post hoc tests. The post hoc analyses showed clearly that no significant difference exist between the different dosage treatments for the vein wall thickness at the required level of 0.05.

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Variable and Source	Df	MS	F	η^2
Vein wall thickness				
Dosage treatment	3	0.17	0.85	0.021
Time	1	0.28	1.44	0.012
Dosage treatment* Time	3	0.53	2.71*	0.064
Error	120	0.20		

TABLE 5 : ANOVA for Vein Wall Thickness as a Function of Dosage Treatment and Time of Scoring.
* $p < 0.01$. Df = degrees of freedom; MS = mean score; F = distribution; η^2 = Eta squared.

Group	Dosage Treatment	Month			Year			Total	
		n	Mean	SD	N	Mean	SD	Mean	SD
A	4 mL 1% STS	16	2.63	0.50	16	3.25	0.45	2.94	0.56
B	8 mL 1% STS	16	3.00	0.73	16	3.50	0.63	3.25	0.72
C	4 mL 3% STS	16	3.00	0.52	16	3.31	0.70	3.16	0.63
D	8 mL 3% STS	16	2.94	0.68	16	2.88	0.81	2.91	0.73
	Total	64	2.89	0.62	64	3.23	0.68	3.06	0.67

TABLE 6 : Descriptive Statistics for Lumen Filling Percentage as a Function of Dosage Treatment and Time of Scoring.
 n = number of patients per subset (group); SD = standard deviation.

Variable and Source	df	MS	F	η^2
Lumen Filling Percentage				
Dosage Treatment	3	0.90	2.20	0.052
Time	1	3.78	9.28*	0.072
Dosage Treatment* Time	3	0.72	1.77	0.042
Error	120	0.41		

TABLE 7 : ANOVA for Lumen Filling Percentage as a Function of Dosage Treatment and Time of Scoring.
* $p < 0.01$. Df = degrees of freedom; MS = mean score; F = distribution; η^2 = Eta squared.

Group	Dosage Treatment	Month			Year			Total	
		n	Mean	SD	N	Mean	SD	Mean	SD
A	4 mL 1% STS	16	1.44	0.51	16	3.06	0.68	2.25	1.02
B	8 mL 1% STS	16	2.31	0.70	16	3.38	0.72	2.84	0.88
C	4 mL 3% STS	16	2.13	0.89	16	2.88	0.81	2.50	0.92
D	8 mL 3% STS	16	2.63	0.89	16	2.94	0.68	2.78	0.79
	Total	64	2.13	0.86	64	3.06	0.73	2.59	0.93

TABLE 8 : Descriptive Statistics for Vein Diameter Reduction as a Function of Dosage Treatment and Time of Scoring.
 n = number of patients per subset (group); SD = standard deviation.

Lumen

Table 6 shows the means and standard deviations for the lumen filling percentage separately for the four dosage treatments and time of scoring groups, i.e., month versus year.

Table 7 shows that there was no significant interaction between dosage treatments and time of scoring on lumen filling percentage ($p = 0.048$).

The main effect of dosage treatments was also nonsignificant on the lumen filling percentage ($p = 0.092$).

Inversely, the main effect of scoring time was significant on the lumen filling percentage, $F(1,120) = 9.28$, $p < 0.05$.

Eta for the scoring time was approximately 0.26 indicating a medium effect size.

Vein diameter reduction

Table 8 shows the means and standard deviations for the vein diameter reduction separately for the four dosage treatments and time of scoring groups, i.e., month versus year.

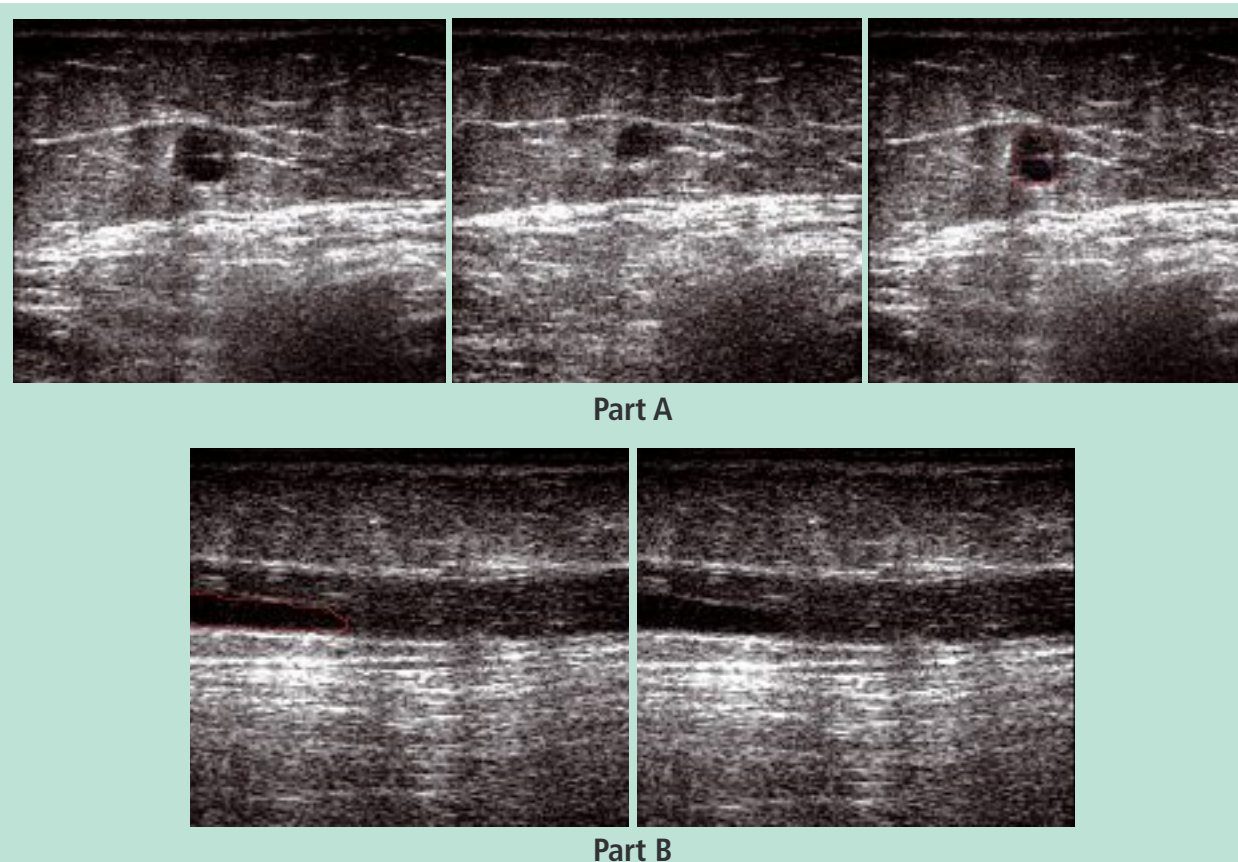


FIGURE 1 : Ultrasound imaging of lumen filling at 75% that shows minimal wall thickness (Part A) and non-sclerosed focal area (Part B).

Variable and Source	df	MS	F	η^2	p value
Vein Diameter Reduction					
Dosage Treatment	3	2.40	4.34*	0.098	< 0.01
Time	1	28.13	50.94**	0.298	< 0.001
Dosage Treatment* Time	3	2.44	4.42*	0.099	< 0.01
Error	120	0.55			

TABLE 9 : ANOVA for Vein Diameter Reduction as a Function of Dosage Treatment and Time of Scoring.

* $p < 0.001$. df = degrees of freedom; MS = mean score; F = distribution; η^2 = Eta squared.

Table 9 shows that there was a significant interaction between dosage treatments and time of scoring on vein diameter reduction ($p = 0.006$). Eta for the interaction was approximately 0.31, which can be considered as a medium effect [8].

There was, also, a significant main effect of dosage treatments on vein diameter reduction, $F(3,120) = 4.34$, $p < 0.01$.

Eta for dosage treatments was approximately 0.31, which, according to Cohen (1988), is a medium effect. Furthermore, there was a significant main effect of scoring time on vein diameter reduction, $F(1,120) = 50.94$, $p < 0.001$.

Eta for scoring time was approximately 0.54 indicating a large effect.

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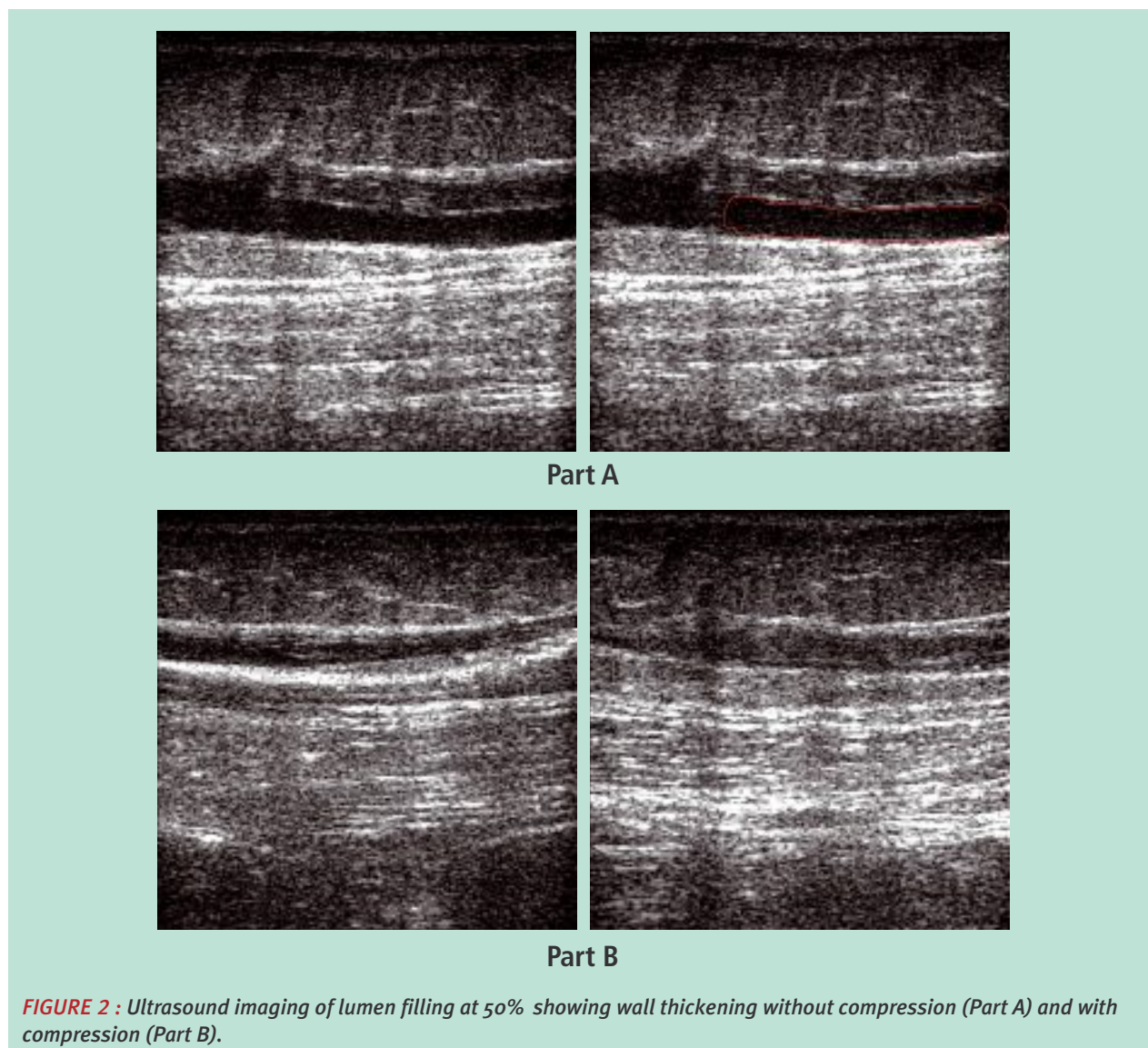


FIGURE 2 : *Ultrasound imaging of lumen filling at 50% showing wall thickening without compression (Part A) and with compression (Part B).*

Levene's test for homogeneity of variance showed that the vein diameter reduction variances can be assumed equal ($p = 0.403$) therefore post hoc Tukey HSD tests were used and indicated that Group A had significantly lower overall score compared with group B and D ($p < 0.05$). There was no significant difference in the vein diameter reduction between any other groups ($p > 0.05$).

No complications were reported in this study.

Discussion

For decades, compression ultrasound and echogenicity have been accepted as the most reliable diagnostic technique for to assess vein sclerosis: however, they may not be accurate assessment techniques.

The lack of accepted variables for evaluating the efficacy of foam sclerotherapy and the vast range of efficacy criteria described in the published literature were factors that prompted the 2nd European Consensus Meeting on Foam Sclerotherapy (2nd ECMFS) in 2006 [9]. At this meeting a consensus on criteria for evaluating the effects of foam sclerotherapy was reached.

These criteria included occlusion (length of occlusion, flow/no flow, reflux, the diameter of the vein, morphologic changes, and absence of vein).

However, a consensus could not be reached on how to use these criteria in establishing a grading system for determining successful treatment.

The grading system proposed at the 2nd ECMFS rated treated veins on a scale of zero through 2: no success = 0, partial success = 1, and full success = 2 [9].

Not only is this a narrow grading system that does not allow for gradients of success, the criteria for each grade are somewhat ambiguous, creating substantial grey areas between grades. For example, a criterion for a grade of zero (no success) is the presence of complete or incomplete patency, while a criterion for a grade of 1 (partial success) is partial occlusion of the treated vein.

The lack of clear distinctions between grades precludes the standardization of this and similar systems.

The scoring system investigated in this study is in alignment with findings of the 2nd ECMFS.

It examines the most relevant criteria identified at that meeting (i.e., lumen filling [occlusion], vein diameter reduction, and vein wall thickness) assessed on images captured during ultrasonic scanning.

This scoring system adds specificity to these criteria missing in the previously proposed grading system. Scoring the efficacy of foam sclerotherapy based on the presence of vein wall thickness and the calculation of percentages for lumen filling and vein diameter reduction provide discreet scale gradients that are not reliant on individual interpretation; therefore, this system can be standardized.

In all 64 GSVs evaluated in this study, the treated veins exhibited a certain degree of phlebo-reaction after 1 month post-injection. The B-scan images over the ROI are shown in **Figure 1**.

The analysis of scores derived from these images showed that there was significant interaction between at least one variable (i.e., dosage treatment, time of scoring) or the combined variables for each parameter (i.e., vein wall thickness, percentage of lumen filling, percentage of diameter reduction). These significant interactions were shown to have large or medium main effects based on the Eta findings.

Most importantly, there was a significant interaction between the dosage treatments and time of scoring for the total score. In addition, each variable had a significant main effect on total scores. The Eta findings for each interaction signify large to medium effects, indicating that there is a close association between these variables and the total scores. Therefore, the total scores reflect the changes that occurred within the treated veins.

While this scoring system reflects the degree of phlebo-reaction captured on ultrasound images, reflux and flow should still be evaluated while scanning the treated vein during clinical evaluation. In addition, image measurements are taken in a 2-D space so may vary slightly from actual dimensions.

In this study, poorly defined boundary between the vessel walls and the lumen in some scan images made it difficult to measure the wall thickness, so the averaging area was selected conservatively to decrease margin of error. However, this should not significantly alter our findings.

Conclusion

The ultrasound sclerosis score is significantly affected by STS dosage, time of scoring, and interaction between the two factors.

Ultrasonographic GSV sclerosis images can be differentiated by their characteristic features of wall thickness, endoluminal filling, and vein diameter reduction.

The ultrasound sclerosis score is useful in assessing the success of vein sclerosis and in evaluating outcomes.

More studies are needed with other sclerosants to determine if USSS is effective in assessing successful sclerosis after treatments other than STS.

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