FULL TITLE

A new automated system for the preparation of sclerosant foam: a study of the physical characteristics produced and the device settings required

SHORT TITLE

New sclerosant foam preparation system

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AUTHOR AFFILIATIONS

ENRIC ROCHE (1,2), RAMON PONS (3), ORIOL ROCHE (4), ANTONI PUIG (2)

1. Vascular surgery. Hospital Universitari Sagrat Cor & General de Catalunya. Barcelona. Spain

2. Vascular surgery. Clínica Vascular Barcelona. Barcelona. Spain

3. Institut de Química Avançada de Catalunya. IQAC-CSIC. Barcelona. Spain

4. Medical Physics and Biomedical Engineering. University College London. London. UK.

CORRESPONDENCE

ENRIC ROCHE

Address: Oliana, 27 bajos. 08006, Barcelona, Spain

25 Mobile: +34607995620. Email: eroche@vbdevices.com

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27 **DECLARATIONS**

28 **Conflict of interest:** ER is founder and main shareholder of VB Devices, the company developing
29 the medical device described herein. RP and OR worked under contract to perform the foam
30 studies. AP is a minority shareholder of VB Devices.

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40 ABSTRACT

41 OBJECTIVES

42 To determine the quality of sclerosant foam produced with an automated preparation system with
43 multiple combinations of sclerosing agents, gases, and device settings.

44 METHODS

45 Single-use mixing capsules filled with air or O₂/CO₂ and polidocanol (0.25%, 1% or 3%) or sodium
46 tetradecyl sulphate (STS) (0.2% or 1%) were coupled to a customized magnetic stirrer. Stirring
47 speed and time were adjusted between 1500 and 4000 rpm and 30 and 60 seconds, respectively,
48 and characteristics of the foam produced were measured: half-life, bubble diameter, and gas-to-
49 liquid ratio.

50 RESULTS

51 With optimized device settings, the following foam characteristics were obtained: half-life range,
52 1.4±0.9 to 5.2±0.6 min; bubble diameter, 84±14 µm to 119±6 µm; and gas-to-liquid ratio, 5:1 to
53 7:1. STS foam was quicker to form than POL but faster to degrade. Foams with low sclerosant
54 concentrations and O₂/CO₂ required higher speed and longer time.

55 CONCLUSIONS

56 Suitable foam characteristics could be obtained with all combinations of sclerosing agent,
57 concentration, and gas.

Introduction

Over the past twenty years, we have seen more widespread use of foam sclerotherapy for the treatment of varicose veins.¹ Since the publication of Cabrera et al's results in venous malformations,^{2,3} followed by Tessari's⁴ foam preparation technique, foam sclerotherapy has been widely adopted in the treatment of varicose veins. Multiple papers and international consensus meetings and guidelines have established foam sclerotherapy as an important additional treatment (to surgical or endovenous procedures) for varicose veins;^{5,6} it may also be considered as a first-line treatment in cases of recurrent varicose veins, or in the treatment of elderly patients.⁷

However, variability in the method used and potential safety concerns pushed the scientific community to determine a standardized technique and promote the use of nitrogen-free foam over air. Hesse,⁸ Morrison,⁹ and other authors^{10,11,12} showed that physiological foam gases were associated with fewer adverse events (eg migraine, visual disturbances, thoracic pressure, and neurological events) than air-based foams, yet air-based foams are generally easier to produce. Although the need for a nitrogen-free foam is debated, some indications such as venous malformations – which require a high volume of sclerosant – or patent foramen ovale are arguments in favor of physiological gas.¹³ Tessari's method of foam production is relatively simple and affordable, but in the case of physiological gas, it can be somewhat awkward as manipulation of the connections to the gas mix bottle is required. In addition, producing a foam from a low concentration of sclerosant – which is preferable in cases of small varicosities – is extremely difficult.

In view of the limitations of the established methods, in 2013, we developed an automatic stirrer system with a disposable sterile gas capsule. An initial comparative study found that it produced foam with very high gas-to-liquid ratios and a longer half-life than that produced using Tessari's method.¹⁴ Based on the optimal characteristics of foam (a half-life of around 2 minutes, microfoam

bubbles [around 100 micron diameter], and a gas-to-liquid ratio of 4 to 7:1),^{5,15} we aimed to test the performance of a newer version of this automated system in producing sclerosant foam, using multiple concentrations of the sclerosants polidocanol (POL) and sodium tetradecyl sulphate (STS) mixed with air or physiological gas. We assessed the characteristics of the resulting foam to identify how changes in the components (type and concentration of surfactant, gas phase [air or O₂/CO₂]) and system settings (stirring speed and stirring time) affected foam production. These data helped to determine program settings for the device to ensure consistent production of high-quality foam.

Material and Methods

Device

The automated system consists of a dome-shaped capsule positioned atop an adapted magnetic stirrer (VB Devices, Barcelona, Spain) (**Figure 1**) [insert Figure 1]. Capsules have a port, with a luer lock for introduction of the sclerosing agent and subsequent removal of the foam. They contain a circular whisk-like rotating element and have a removable seal on top for pressure equilibration prior to removal of the foam. The magnetic stirrer has two main adjustable settings: *stirring speed* and *stirring time*.

Gases and surfactants

Physiological gas capsules were filled with a 70%/30% mixture of O₂/CO₂ from a pressurized gas bottle. The surfactant solutions tested were Aethoxysklerol (polidocanol) 0.25%, 1% and 3%, (Kreussler Pharma, Germany) and VEINFIBRO (STS) 0.2% and 1% (STD Pharmaceuticals, UK).

Procedure and settings

Experiments were performed at the Institut de Química Avançada de Catalunya (IQAC-CSIC, Barcelona, Spain). Capsules were loaded with 2 mL of surfactant solution through the side luer-

lock entrance, using a syringe that was weighed both empty and after loading the liquid. Without removing the syringe, the stirrer was set to the specified speed and time (range: 1500 to 4000 rpm, and 30-60 seconds). Upon completion, the stirring speed was decreased, the top seal opened, and the foam withdrawn up to the 10 mL mark using the same attached syringe. This withdrawal took between 10 and 20 seconds, after which the timer was started. The syringe was left in an upright position in front of a camera (ToUcam PRO II, Philips, Eindhoven, Netherlands) and pictures were taken at different times (30, 60, 90, and 120 seconds and every minute thereafter until more than half the liquid volume had drained). With the syringe removed, the capsule was immediately placed under the microscope (Zeiss, Jena, Germany) and three images taken (PowerShot S90, Canon, Japan, adapted to the microscope) of three different locations of the flat bottom of the capsule, within the shortest possible time, typically <1 minute. A circular light source was used to produce the best contrast images possible. The foam was then aspirated and the syringe weighed to calculate the total amount of surfactant solution present in the sampled foam.

Capsules, as a default, contain room air. For experiments using O₂/CO₂, capsules were filled via teflon tubing through the side port, at a flow of 14±1 cm³/s for 30 s, about 15 times the volume of the capsule, to ensure the capsule was completely filled. Apart from this step, the procedure to prepare the foam was identical for both gas types.

The full combination of conditions tested is shown in **Table 1**. Speeds ranged from 1500 rpm to 4000 rpm, and times ranged from 30 to 60 seconds. Initially, polidocanol (0.25%, 1% and 3%) plus air or O₂/CO₂ was stirred at 4000 rpm for 30 seconds, 45 seconds, and 60 seconds. Based on the initial results (high gas ratios with high speed stirring), further polidocanol experiments were conducted at 1% and 3% polidocanol, air, and a lower speed of 2000 rpm to test the influence of speed on the ratio. Fewer experiments were carried out for STS, primarily because we use polidocanol in our everyday practice. As STS foam is generally easier to produce (albeit less stable),

we tested its production at lower speeds, limiting experiments to a maximum of 3000 rpm. All experiments were performed in triplicate.

Sclerosant type	Sclerosant concentration	Gas	Stirring Speed, rpm	Stirring time, seconds
Polidocanol	0.25%	Air	4000	30
Polidocanol	0.25%	Air	4000	45
Polidocanol	0.25%	Air	4000	60
Polidocanol	0.25%	O ₂ /CO ₂	4000	30
Polidocanol	0.25%	O ₂ /CO ₂	4000	45
Polidocanol	0.25%	O ₂ /CO ₂	4000	60
Polidocanol	1%	Air	4000	30
Polidocanol	1%	Air	4000	45
Polidocanol	1%	Air	4000	60
Polidocanol	1%	Air	4000	30
Polidocanol	1%	Air	4000	45
Polidocanol	1%	Air	4000	60
Polidocanol	3%	Air	4000	30
Polidocanol	3%	Air	4000	45
Polidocanol	3%	Air	4000	60
Polidocanol	3%	Air	4000	30
Polidocanol	3%	Air	4000	45
Polidocanol	3%	Air	4000	60
Polidocanol	1%	Air	2000	30
Polidocanol	3%	Air	2000	30
Polidocanol	1%	Air	1500	30
Polidocanol	3%	Air	1500	30
STS	0.2%	air	1850	60
STS	0.2%	air	2000	30
STS	0.2%	O ₂ /CO ₂	2000	30
STS	0.2%	O ₂ /CO ₂	2500	45
STS	0.2%	O ₂ /CO ₂	3000	30
STS	1%	Air	1500	30
STS	1%	Air	1750	30
STS	1%	Air	2000	30
STS	1%	Air	2000	45
STS	1%	O ₂ /CO ₂	1750	30
STS	1%	O ₂ /CO ₂	1750	60
STS	1%	O ₂ /CO ₂	2000	30

Table 1. Conditions initially tested with the automated foam production system. Each condition was tested in triplicate. Based on initial results, further comparisons and statistical analysis were restricted to conserve resources.

Measurement of outcome variables

The outcome variables measured were: 1) foam stability, or half-life ($T_{1/2}$), defined as the time when half the liquid composing the foam had drained in a quiescent upright syringe containing the foam.

The height of the liquid was measured from photographs, after size calibration, to determine the drained volume. The relative volume was calculated by dividing the drained volume by the total liquid volume contained in the syringe, which in turn was obtained from the weight of the fully loaded syringe minus that of the empty syringe; 2) gas-to-liquid ratio (R), determined using the total volume drawn from the capsule and the liquid volume (determined by weighing). Being V the total volume and L the volume of liquid, the gas-to-liquid ratio corresponds to $(V-L):L$; and 3) foam bubble diameter, measured by coupling a Canon Powershot S90 camera to a Zeiss microscope using a 10x ocular and a 2.5x objective. The number of measured bubbles was typically above 200 per picture; three pictures were taken per sample.

Statistical analysis

Experiments were performed with successive replicates except for the final evaluation of the optimal conditions, where the full set of measurements and replicates was randomized. Data analysis was performed with one-way ANOVA, using the software Microcal Origin 5.0, to check for the effect of the controlled variables on the resulting magnitudes. If there was no significant difference between the means, the different sets were mixed to determine their mean and mean deviations to evaluate the corresponding confidence intervals. In the evaluation of bubble diameter, median measurements were used for comparison (and one-way ANOVA).

Results

In general, we observed that foams made with STS appeared to form more quickly, but also degrade more quickly than polidocanol, and foams made from low sclerosant concentrations or O_2/CO_2 required higher speed and longer time to reach the same quality. **Table 2** shows the results for the foam characteristics obtained with the optimized device settings. Speeds are presented as

high-medium-low to preserve intellectual property. Details on the most relevant trends observed in half-life, bubble diameter and gas-to-liquid ratio are summarized below.

Program number	Sclerosant concentration and gas	Stirring speed	Stirring time	Bubble diameter	Half-life	Ratio
Polidocanol						
1	0.25% POL + air	High	45 sec.	102±20 µm	4.4±0.8 min.	5.9(±1.3):1
2	1% POL + air	Low	30 sec.	86±14 µm	2.4±0.9 min.	5.1(±3.3):1
2	3% POL + air	Low	30 sec.	116±24 µm	5.2±0.6 min.	7.4(±3.7):1
3	0.25% POL + O ₂ /CO ₂	High	45 sec.	116±10 µm	1.8±0.3 min.	6.0(±0.3):1
4	1% POL + O ₂ /CO ₂	High	30 sec.	117±17 µm	2.1±0.5 min.	6.9(±0.9):1
4	3% POL + O ₂ /CO ₂	High	30 sec.	119±6 µm	2.5±0.2 min.	7.6(±0.6):1
STS						
5	0.2% STS + air	Medium	30 sec.	84±14 µm	3.0±0.9 min.	6.2(±4.3):1
6	1% STS + air	Low	30 sec.	86±13 µm	1.4±0.9 min.	4.4(±2.9):1
7	0.2% STS + O ₂ /CO ₂	High	45 sec.	93±21 µm	1.8±0.4 min.	6.0(±0.4):1
8	1% STS + O ₂ /CO ₂	Medium	30 sec.	89±20 µm	1.4±0.7 min.	7.3(±3.6):1

Table 2. Device settings for foam production with the automated device, according to the sclerosant and gas used, and the physical characteristics of the foam produced. Users select stirring speed (high, medium or low) and time. Figures are given as median and 95% confidence intervals according to Student t test.

It is suggested that these program settings are suitable for the following conditions:

Program 1. Air + polidocanol <1%.

Program 2. Air + polidocanol ≥1%

Program 3. O₂/CO₂ + polidocanol <1%.

Program 4. O₂/CO₂ + polidocanol ≥1%

Program 5. Air + STS <0.5%.

Program 6. Air + STS ≥0.5%.

Program 7. O₂/CO₂ + STS < 0.5%.

Program 8. O₂/CO₂ + STS ≥0.5%

179

180 **Half-life**

181 With optimized settings, mean foam half-life ranged from 1.4 ± 0.7 (1% STS plus O_2/CO_2) to 5.2 ± 0.6
 182 minutes (3% POL plus air) (**Table 2**).

183 *Polidocanol: effect of stirring time on half-life*

184 With polidocanol 1% and 3%, stirring time did not affect the stability of foam produced, and 30
 185 seconds was sufficient to create a stable foam with air or O_2/CO_2 (**Table 3**). However, at the lowest
 186 surfactant concentration (0.25%), there was a significant correlation between stirring time and
 187 half-life ($r=0.93$ for air foam; $r=0.75$ for O_2/CO_2). **Figure 2** plots the differences in half-life according
 188 to stirring time for 0.25% POL foam.

189

Stirring time	Half-life ($T_{1/2}$), minutes		
	POL 0.25%*	POL 1%	POL 3%
Air			
30 s	2.4	4.6	5.6
45 s	2.7	4.2	5.1
60 s	3.0	3.5	5.9
Average	2.7	4.1	5.5
O_2/CO_2			
30 s	1.5	2.4	1.9
45 s	1.8	1.7	1.8
60 s	1.8	2.8	1.6
Average	1.7	2.3	1.7

Table 3. Mean half-life of foam produced from polidocanol plus air or O₂/CO₂. The results stratified by stirring time were obtained with a stirring speed of 4000 rpm. *Only 0.25% polidocanol showed a statistically significant association between stirring time and T_½.

[insert Figure 2]

Polidocanol: effect of stirring speed on half-life

Foam stability was affected by stirring speed. For polidocanol, when the stirring speed was increased, the half-life increased from 2.8 to 4.1 minutes for 1% POL plus air ($p=0.028$), and from 3.1 to 5.6 minutes for 3% POL plus air ($p=0.014$). With STS, an increase in stirring speed also resulted in a longer half-life (even despite a decrease in sclerosant concentration), particularly for air foam, where half-life increased from 1.4 to 3.0 minutes.

Gas-to-liquid ratio

The gas-to-liquid ratio (R) ranged from 5:1 to 7:1 (**Table 2**). At 0.25% polidocanol, no significant differences were seen in R when all experiments were compared together (**Table 4**). Discriminating by gas phase, there was a slight positive correlation between stirring time and R when air was used but not so for O₂/CO₂. This disparity may not be physically relevant.

At 1% polidocanol, there were no significant differences in R, either when taking all the experiments together or discriminating by gas. At 3% polidocanol, although there were significant differences in R when comparing all experiments, when discriminating by gas phase, there were no significant differences (**Table 4**).

POL 0.25%	POL 1%	POL 1%	POL 3%	POL 3%
4000 rpm	4000 rpm	2000 rpm	4000 rpm	2000 rpm
Gas: liquid ratio				

Air					
Average	5.6:1	7.6:1		9.0:1	
30 s	5.4:1	8.0:1	5.1:1	8.2:1	5.0:1
45 s	5.6:1	7.4:1		8.9:1	
60 s	5.9:1	7.4:1		9.9:1	
O ₂ /CO ₂					
Average	5.8:1	7.7:1		6.7:1	
30 s	5.7:1	8.0:1		6.6:1	
45 s	5.9:1	6.5:1		6.9:1	
60 s	5.9:1	8.4:1		6.5:1	

Table 4. Ratios obtained at high stirring speed with 0.25%, 1%, and 3% polidocanol, and at low stirring speed for 1% and 3% polidocanol. Higher concentrations were affected by stirring speed, higher speed leading to an increased gas-to-liquid ratio.

In experiments with 1% and 3% polidocanol, stirrer speed affected R: at 4000 rpm, high R values were obtained (around 8:1); when stirrer speed was reduced to 2000 rpm, R also decreased (around 5:1) (**Table 4**). The differences in gas-to-liquid ratio at these two speeds were statistically significant (POL 1%, $p=0.034$; POL 3%, $p=0.016$).

There was a correlation between R and $T_{1/2}$. **Figure 3** shows this correlation, taking together all the results for polidocanol (all surfactant concentrations and stirring speeds and times): the greater the gas-to-liquid ratio, the greater the half-life. The observed increase in half-life at high gas ratios could be due to the change of mechanism for drainage in drier foams (see discussion).

[insert Figure 3]

In the case of STS, there was no clear correlation between R and $T_{1/2}$ when air was used. This is probably due to the short range of ratios observed for those samples (4.0 to 7.3). However, the samples prepared with O_2/CO_2 seemed to show a strong increase in $T_{1/2}$ at high gas ratios (**Figure 4**).

[insert Figure 4]

Looking at the effect of polidocanol concentration (0.25%, 1% or 3%) on R and $T_{1/2}$, the concentration appeared to have a moderate or no effect when O_2/CO_2 was used, but a significant effect when air was used: both R and $T_{1/2}$ increased as polidocanol concentration increased for experiments performed at 4000 rpm. It is debatable whether a straight line or a curve should reflect these behaviors; a straight line can be drawn through the error bars but there is a systematic positive bias of the 1 % concentration (**Figure 5**).

[insert Figure 5]

Bubble diameter

Bubble diameter ranged from 84 μm with 0.2% STS and air to 119 μm with 3% POL and O_2/CO_2 . No clear trends were observed, and some results even appeared somewhat contradictory. At 0.25% polidocanol there were statistically significant correlations: when air was used, increased stirring time led to smaller bubble size (as would be expected), while the opposite occurred with O_2/CO_2 . Mean bubble size was smaller with air than with O_2/CO_2 .

At 1% polidocanol there were no significant differences in bubble size with stirring time or gas phase. The distribution of bubble diameter for foams produced with 1% polidocanol, O_2/CO_2 , at 4000 rpm for 30s are presented in **Figure 6** [insert Figure 6]. It is clear that bubble diameter increased with time, however, no bubbles above 800 μm were observed at 2 minutes. At 3% polidocanol, there were no differences attributable to stirring time but there were some differences attributable to gas phase: contrary to what happened with 0.25% surfactant, the mean bubble size was larger with air than with O_2/CO_2 .

Polidocanol foams from 1% and 3% sclerosant plus air were compared at two different stirring speeds. Surprisingly, the increase in stirring speed resulted in a significant increase in bubble size for both concentrations (POL 1%, $p=0.001$; POL 3%, $p=0.018$).

Overall, STS bubbles had a smaller diameter than those of polidocanol.

Discussion

The automatic system tested here was able to create a uniform foam suitable for clinical use. Importantly, it was able to do so even at low sclerosant concentrations that usually impede foam production with existing manual systems. This ability is thought to be due to the effective shear exerted on the sclerosant mixture with the automated system, allowing the production of foams, even at very low concentrations, with longer half-lives and higher gas-to-liquid ratios (around 5:1 to 7:1) than typically occur with Tessari's method or the double syringe system (around 3:1 or 4:1). Thus, higher shear stress appears to improve foam formation compared with existing manual methods, particularly with physiological gases.

We found that in air foams, stirring speed was associated with an increased gas-to-liquid ratio and this in turn had a positive effect on the stability. Generally, increased stirring time contributed to more stable foams with 0.25% polidocanol solutions but was not relevant at 1% and 3% polidocanol solutions. In contrast, O₂/CO₂ foams were less stable and not affected (R or bubble size) by stirring time; in many cases, a foam suitable for injection was formed at 30 seconds.

It is well established in the literature that the gas used has an influence on the resulting foam.¹⁶ In our study, air foams had a longer half-life (around 2 minutes) than those made with O₂/CO₂. When we compared the gas-to-liquid ratios produced with air vs O₂/CO₂, there was statistical significance only with 3% polidocanol; indeed, half-life rose to 5.9 minutes.

Stirring speed increased both R and T_½. However, we also observed an increase in bubble size with stirring speed, which was not an expected result; we expected increased speed to produce smaller

bubbles that would result in a more stable foam. A possible explanation lies in the effect of R: an increase in stirring speed produces a bigger uptake of the dispersed gas phase, which increases the elasticity of the foam, reducing the shear on the already formed foam. In some extreme cases, the foam became so elastic that it stopped or altered the movement of the magnetic stirrer. Thus, the more elastic foams (higher R) are likely to have older bubbles that increase in size as they mature. Foams with higher gas-to-liquid ratios had greater stability. A further possible explanation behind this observed foam behavior is the process of drainage, which governs $T_{1/2}$: the higher the gas-to-liquid ratio, the thinner the channels for the liquid to drain between bubbles. Additionally, as the gas ratio increases, and the amount of liquid decreases, the amount of liquid required to form the foam will constitute a relatively higher proportion of the total liquid. Both factors contribute to slowing the flow of liquid.¹⁷ Furthermore, at very high gas ratios, there is no liquid available for drainage until some coalescence takes place and frees some liquid from the films and plateaus. We did not study whether bubble size directly affected $T_{1/2}$, but the correlation between R and $T_{1/2}$ seems to play an important role.

Although our study performed fewer experiments with STS, we did note that STS foams formed more rapidly than polidocanol foams but had a shorter half-life. This may be due to an intrinsic instability of the films formed by ionic (eg STS) as compared with nonionic surfactants (eg polidocanol). Nonionic surfactants produce a dense layer of ethylene oxide polymer that is relatively viscous, providing some elasticity that may prevent rupture of the film.^{18,19,20} In ionic surfactants, the ionic head groups are comparatively small and do not promote significant viscosity; stabilization is based on electrostatic repulsion between the two sides of the film. However, we must consider the limitations of our results: while the reproducibility of the experiments with polidocanol seems reasonable, results from STS foam showed greater variation. A secondary objective of this study, based on the observed foam characteristics, was to define the optimal parameters for stirrer programming. Analysis of our data allowed us to suggest 8 different

programs according to the possible constituents used (See **Table 2** notes). Regarding the sclerosant concentrations, statistical analysis of the data from this study showed little to no differences in foam characteristics at concentrations of polidocanol or STS below 1%, which we interpret as meaning that these different concentrations do not require different settings (**Table 2**). Thus, users of the device should decide on the type of gas (air or O₂/CO₂), type of sclerosant (polidocanol or STS) and concentration of sclerosant (low or high) they wish to use. Once these are determined, the device may be programmed accordingly, and the stirrer is activated until a symbol on the device's display indicates that the foam is ready for withdrawal. These suggested automated programs should minimize variability in the resulting foams.

The present study was designed to study this device and not as a comparative study against other foam pre-mixing systems, namely the polidocanol endovenous microfoam characteristics published by Carugo et al (device unavailable in Europe).¹⁵ However, the bubble distribution characteristics – a gas-to-liquid ratio between 6 and 7 and bubble size around 120 µm – with O₂/CO₂ foams at various sclerosant concentrations (**Figure 6**) were similar to those described by Carugo et al with O₂/CO₂ 1% polidocanol foam, which we consider worth highlighting.¹⁵ Irrespective of this observation, we consider it highly relevant that we were able to produce a uniform foam from low concentrations with polidocanol (0.25%) or STS (0.2%) plus air or O₂/CO₂, given the clinical implications: low-sclerosant-concentration foams are preferable for small varicosities. Watkins²¹ et al demonstrated reproducibility and standardization in the production of foams from 1% and 3% STS by Tessari's method, but the concentrations used in that paper were relatively high according to common practice: such concentrations are generally used for the treatment of medium to large varicose veins. In vascular clinics, however, there is often a higher caseload of varicosities or subdermal spider veins, and substantial scope for improvement in the treatment of these aesthetic conditions.

If we consider that the most common use of sclerotherapy is as a complementary treatment to other surgical or endovenous procedures, then ideally, the foam production system used should offer versatility. If we want to avoid a potential overdose effect in medium or small varicose veins, advisable concentrations would be below 1% for polidocanol and below 0.5% for STS, something which is extremely difficult with other methods. In addition, while Tessari's method with air has been demonstrated to be safe, if the operator elects to use a physiological gas mixture to optimize safety margins, our new automated system provides a convenient method of using O₂/CO₂ in prefilled capsules.

Finally, an additional benefit of a standardized foam production system is that it may prove helpful in further studies on the efficacy of foam sclerosis in treating spider veins or varicosities, as use of a standardized foam could improve the robustness of the scientific method used.

Limitations

The main limitation of our study relates to the number of replicates, though the data appear to coincide with others in the literature regarding the physical characteristics of foam. Fewer experiments were performed with STS than with polidocanol, so these results could be explored further. We focused on polidocanol because we use this sclerosant in our everyday practice, and so we deemed its results to be more clinically relevant. Despite this limitation, in this initial study, we were able to observe consistent patterns in foam characteristics, which allowed us to propose device program settings. The precise values are to some degree arbitrary (for example, a speed of 2000 rather than 1900 or 2100 rpm), and it remains possible that more extensive studies may find significant (or not) differences between settings, allowing slight modifications to the programs: the potential additional of intermediate programs, or merging to give fewer programs.

Conclusion

This automatic foam preparation device was able to consistently produce sclerosant foam suitable for venous injection, within 45 seconds, using air or O₂/CO₂ and polidocanol or STS, even at low concentrations of sclerosant. The device's settings of stirring speed and time can be programmed to ensure that the standard of foam produced with different components is maintained, overcoming the limitations of gas type and surfactant concentration. The versatility, convenience and standardization of this system represent a potential advance in the practice of sclerotherapy.

Figures

Figure 1. Capsule coupled to the adapted stirrer system with a syringe connected. A port at the base of the capsule allows foam withdrawal and a peel-off seal on the top allows air pressure compensation prior to withdrawal.

Figure 2: Correlation between stirring time and foam stability ($T_{1/2}$) for foams produced at 4000 rpm with 0.25% polidocanol plus air ($r=0.93$); or O₂/CO₂ ($r=0.75$).
Abbreviations: min, minutes; $T_{1/2}$, half-life; s, seconds.

Figure 3: Correlation between R (gas to liquid ratio) and half-life ($T_{1/2}$) for 0.25%, 1% and 3% polidocanol solutions with air or O_2/CO_2 stirred at 2000 and 4000 rpm. The lines are fits to the 4000 rpm data (air and O_2/CO_2 , respectively; $r=0.80$ for polidocanol and air, $r=0.87$ for polidocanol and O_2/CO_2).
Abbreviations: min, minutes; R , liquid to gas ratio; rpm, revolutions per minute; $T_{1/2}$, half-life.

Figure 4: Correlation between R (gas to liquid ratio) and half-life ($T_{1/2}$) for 0.2% and 1% STS solutions with air and O₂/CO₂.
Abbreviations: min, minutes; R, gas to liquid ratio; rpm, revolutions per minute; $T_{1/2}$, half-life; STS, sodium tetradecyl sulphate.

Figure 5. Effect of polidocanol concentration (0.25%, 1% or 3%) on R (gas to liquid ratio) and $T_{1/2}$ for foams produced at 4000 rpm with air or O_2/CO_2 . $r=0.96$ for % and $T_{1/2}$ in air foam; $r=0.56$ for % and $T_{1/2}$ in O_2CO_2 foam; $r=0.94$ for % and R in air foam; $r=0.88$ for % and R in O_2CO_2 foam, as calculated on linear regression.

Abbreviations: min, minutes; R, gas to liquid ratio; $T_{1/2}$, half-life.

Figure 6: Foam bubble diameter distribution measured at approximately 40 and 120 seconds. Foams produced with 1% polidocanol, O₂/CO₂, at 4000 rpm for 30s. Abbreviations: rpm, revolutions per minute; s, seconds.

REFERENCES

1. O'Hare JL, Earnshaw JJ. The use of foam sclerotherapy for varicose veins: a survey of the members of the Vascular Society of Great Britain and Ireland. *Eur J Vasc Endovasc Surg*. 2007 Aug;34(2):232-5.
2. Cabrera J, Cabrera J Jr, Garcia-Olmedo MA, et al. Treatment of venous malformations with sclerosant in microfoam form. *Arch Dermatol*. 2003 Nov;139(11):1409-16.
3. Redondo P, Cabrera J. Microfoam sclerotherapy. *Semin Cutan Med Surg*. 2005 Dec;24(4):175-83.
4. Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. *Dermatol Surg*. 2001 Jan;27(1):58-60.
5. Rabe E, Breu FX, Cavezzi A, et al. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology*. 2014 Jul;29(6):338-54.
6. Breu FX, Guggenbichler S, Wollmann JC. 2nd European Consensus Meeting on Foam Sclerotherapy 2006, Tegernsee, Germany. *Vasa*. 2008 Feb;37 Suppl 71:1-29.
7. Coleridge Smith P. Sclerotherapy and foam sclerotherapy for varicose veins. *Phlebology*. 2009 Dec;24(6):260-9.
8. Hesse G, Breu FX, Kuschmann A et al. Sclerotherapy using air- or CO₂-O₂-foam. Post-approval study. *Phlebologie*. 2012; 41. 77-88.
9. Morrison N, Neuhardt DL, Rogers CR, et al. Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. *J Vasc Surg*. 2008 Apr;47(4):830-6.
10. Malvey MA, Asbjornsen C. Transient neurologic event following administration of foam sclerotherapy. *Phlebology*. 2017 Feb;32(1):66-68.
11. Willenberg T, Smith PC, Shepherd A, et al. Visual disturbance following sclerotherapy for varicose veins, reticular veins and telangiectasias: a systematic literature review. *Phlebology*. 2013 Apr;28(3):123-31.

12. Parsi K. Paradoxical embolism, stroke and sclerotherapy. *Phlebology*. 2012 Jun;27(4):147-67.
13. Eckmann DM, Kobayashi S, Li M. Microvascular embolization following polidocanol microfoam sclerosant administration. *Dermatol Surg*. 2005 Jun;31(6):636-43.
14. Roche E, Pons R, Puig A, et al. Feasibility of a new system of standardized foam fabrication and comparison with Tessari's method. In: Accepted Abstracts, 15th Meeting of the European Venous Forum, Paris, France, 26–28 June 2014. *Phlebology*. 2014; 29(8), 543–565.
15. Carugo D, Ankrett DN, Zhao X, et al. Benefits of polidocanol endovenous microfoam (Varithena®) compared with physician-compounded foams. *Phlebology*. 2016 May;31(4):283-95.
16. Peterson JD, Goldman MP. An investigation into the influence of various gases and concentrations of sclerosants on foam stability. *Dermatol Surg*. 2011 Jan;37(1):12-7.
17. Princen HM. Gravitational syneresis in foams and concentrated emulsions. *J. Colloid Interface Sci*. 1990; 134 (1);188-197.
18. Schick MJ, Beyer EA. Foaming properties of nonionic detergent. Journal of the American Oil Chemists' Society. 1963;40 (2); 66-68.
19. Pons R, Rossi P, Tadros TF. Investigation of the Interaction between Emulsions and Suspensions (Suspoemulsions) Using Viscoelastic Measurements. *J. Phys. Chem.*, 1995;99 (33);12624-12630.
20. Pons R, Valiente M, Montalvo G. Structure of Aggregates in Diluted Aqueous Octyl Glucoside/Tetraethylene Glycol Monododecyl Ether Mixtures with Different Alkanols. *Langmuir*. 2010; 26 (4); 2256–2262.
21. Watkins MR, Oliver RJ. Physiochemical properties and reproducibility of air-based sodium tetradecyl sulphate foam using the Tessari method. *Phlebology*. 2017 Jul;32(6):390-396.