Polidocanol foam stability in terms of its association with glycerin


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Abstract

Objectives: Foam sclerotherapy effectiveness mainly depends on the concentration of the sclerosing agent and foam stability. The objective of this study was to determine if the addition of glycerol at different concentrations contributes to the stability of polidocanol foam.

Materials and methods: Control Group: 3% polidocanol. Group 1: polidocanol 3% + glycerin 1.66%. Group 2: polidocanol 3% + glycerin 3.3%. Group 3: polidocanol 3% + Glycerin 5%. Tessari standard method. Five recordings were made for each mixture. Early visual liquefaction time and half liquid time decay were recorded in seconds. Microscopic measurement of the foams. Mixtures surface tension measurement (N/m).

Results: Early visual liquefaction: Control Group: 27 (+ 3.11); Group 1: 67.8 (+ 6.49); Group 2: 48.6 (+ 8.2); and Group 3: 35.8 (+ 4.49). Half-liquid time: Control: 129.2 (+ 11.00); Group 1: 260.4 (+ 18.99); Group 2: 224.6 (+ 13.03); and Group 3: 189.2 (+ 8.52). Bubbles/mm²–diameter–wall thickness: Control: 68–98 μm–7 μm; Group 1: 189–60 μm–9 μm; Group 2: 76–92 μm–12 μm; and Group 3: 49–112 μm–20 μm. Surface tension: Control = 5.54 N/m; Group 1 = 5.45 N/m; Group 2 = 5.35 N/m; and Group 3 = 5.21 N/m.

Conclusions: Small amounts of glycerin highly increase the stability and quality of polidocanol foam. This simple chemical method is easily reproducible and applicable.

Keywords: foam; sclerotherapy; polidocanol; glycerin; stability

Introduction

Foam sclerotherapy is a well-recognized treatment for varicose veins. In our environment, polidocanol is the most widespread sclerosant agent and the Tessari method is the technique that is most widely used for its simplicity and reproducibility. Treatment efficacy depends on many variables, including the correct technique and indication, as well as the use of an adequate concentration in each case. The Tessari method delivers a short half-life foam that necessitates prompt application, thereby conditioning the treatment. Foam stability is achieved by a complex balance involving the physical–chemical characteristics of the fluids and gases used. The fluid’s surface tension and – of course – its manufacturing energy are particularly important. The higher the manufacturing energy and the lower the surface tension are, the greater the foam stability. A polidocanol foam product, which is presumably more stable due to the pressure at which the foam is produced and the kind of gas used, has been described. Research has also been conducted on the polidocanol foam stability and the kind of material used for its manufacture. Lastly, some papers on the influence of the gases used and the addition of glycerin to another sclerosing agent – sodium tetradecyl sulphate – have been recently published.
A theoretical investigation led us to consider that the use of a tensoactive substance (substance-modifying surface tension) such as glycerin, associated with polidocanol, would produce more stable foam. Glycerin (or glycerol) has shown to be safe when administered intravenously; as a matter of fact, there is a glycerin-based weak sclerosant – chromated glycerin. It is soluble in water and alcohol and, therefore, absolutely chemically compatible with polidocanol.

The aim of this work is to describe polidocanol foam stability variation based on its association with glycerin at different concentrations, as well as the physical study of the surface tension of solutions and the microscopic observation of the different bubbles obtained.

Materials and methods

We designed a trial in which we manufactured 3% polidocanol foam (Aethoxysclerol Kreussler Pharma, Postfach, Wiesbaden, Germany) with the Tessari method. We used two silicone-free 5 mL syringes (BD Discardit II, Becton Dickinson, Helsingborg, Sweden) and a three-way stopcock (BD Connecta, Becton Dickinson), and put 1 mL of 3% polidocanol in one syringe and 4 mL of ambient air in the other. Twenty passes were performed in the standard way to obtain the foam. This trial with polidocanol 3% alone is considered as the Control Group. At the same time, and in successive order, we produced foam with 1 mL of polidocanol, adding 0.2 mL of 10%, 20% and 30% glycerin (compounding formulation at the Hospital Clinico San Carlos: glycerin + 3% Aethoxysclerol), creating three trial groups: Group 1: 1 mL of 3% polidocanol + 0.2 mL of 10% glycerin (3% polidocanol + 1.66% glycerin); Group 2: 1 mL of 3% polidocanol + 0.2 mL of 20% glycerin (3% polidocanol + 3.33% glycerin); Group 3: 1 mL of 3% polidocanol + 0.2 mL of 30% glycerin (3% polidocanol + 5% glycerin) (Table 1).

The trial was conducted by immediately introducing the foam made into graduated two glass test tubes (Graduated Essay Tube Pyrex Glass, Code 200461416, Instrumentacion Cientifica Tecnica, SL, Lardero, La Rioja, Spain). One test tube (on the left side of the picture) always had the Control Group and the other (right side) had the various groups with different concentrations (Figure 1). Early visual foam liquefaction time (begins to observe a liquid phase in the tube) and liquefaction time at half-volume, 0.5 mL or ‘half-life’ of the foam were measured like in other works. For this, photographs were taken every 10 seconds (±5 seconds) controlled by a digital timer. The variability in the chronometer is due to focus and flash recharge. The trials were performed by two experienced surgeons who conducted five tests in each group, randomly alternating between the control group and any trial group for less variability. The tubes and disposable material were renewed for each test. Room temperature was controlled at 23°C.

We also made a microscopic observation of different foams (immediately after the generation) with a

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**Table 1** Polidocanol/glycerin foam time decay (seconds)

<table>
<thead>
<tr>
<th>Test 1</th>
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<table>
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<tr>
<th>Mean (±)</th>
<th>(± 3.11)</th>
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<th>(± 18.99)</th>
<th>(± 8.2)</th>
<th>(± 13.03)</th>
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<tr>
<td>Early visual liquefaction time</td>
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slide cover in order to have a single bubble layer
and a bi-dimensional observation, with a scale of
500 μm (Eclipse Ti, Nikon Instruments Inc.,
Europe B.V., Amstelveen, Netherlands). Photos-
graphs were taken and the number of bubbles per
mm², mean diameter in microns and bubble wall
thickness in microns were analysed in each group.
Lastly, the surface tension of the solutions in the
various groups was measured. The technique
used was the Du Nouy ring method of 25 mm of
diameter, calibrated with distilled water at a con-
trolled temperature of 25°C, expressed in inter-
national Newton/meter (N/m) units. This method
utilizes the interaction of a ring with the surface
being tested. The ring is submerged below the inter-
face and subsequently raised upwards. As the ring
moves upwards it raises a meniscus of the liquid.
Eventually, this meniscus tears from the ring and
returns to its original position. Prior to this event,
the force exerted passes through a maximum value
(Scale Ohaus Explorer® Pro, Ohaus Europe GmbH,
Nänikon, Switzerland, model EP 64CN: readability
0.1 mg/verification interval 1 mg). Figure 2.

In the statistical analysis the values are expressed
as mean and standard deviation since the distri-
bution of the variables in each of the groups
showed no asymmetry, and non-parametric test
was applied due to the small sample sizes of the
groups. The statistical package was the SPSS 15;
data were analysed independently by means of
Mann-Whitney U test (the simultaneous completion
of the trial tests does not lead to that are dependent
on a common factor). The groups were compared
with each other using the Kruskal–Wallis test.

Results
Following the 15 tests, an early visual liquefaction
time of 23–30 seconds (mean 27 ± SD 3.11) was
obtained in the Control Group (1 mL of 3% polido-
canol). Half-life of 100–140 seconds (mean 129.2 ±
SD 11.00). For Group 1 (1.66% glycerin), early visual
liquefaction time: 60–75 seconds (mean 67.8 ± SD 6.49).
Half-life: 240–280 seconds (mean 260.4 ± SD 18.99). For
Group 2 (3.33% glycerin), early visual lique-
faction time: 40–60 seconds (mean 48.6 ± SD 8.2).
Half-life: 210–240 seconds (mean 224.6 ± SD 13.03).
For Group 3 (5% glycerin), early visual lique-
faction time: 30–40 seconds (mean 35.8 ± SD 4.49).
Half-life: 180–200 seconds (mean 189.2 ± SD 8.52).
Statistical analysis showed significant differences,
between the Control Group and the different
Groups (Table 2).

The result of the microscopic observation of foam
in the Control Group was: 68 bubbles/mm², mean
diameter = 98 μm (± SD 23) and mean wall
thickness = 7 μm (± SD 2). Group 1: 189 bubbles/
mm², mean diameter = 60 μm (± SD 15), and
mean wall thickness = 9 μm (± SD 2). Group 2:
76 bubbles/mm², mean diameter = 92 μm (± SD 18) and mean wall thickness = 12 μm (± SD 4).

Figure 1 Timing mode measurement of foam liquefaction. Note the absence of visual liquefaction in the test tube on the right, compared with the left marked as Control (polidocanol 3%)

Figure 2 Measurement technique for the surface tension by direct pull, known as the Du Nouy ring method

Table 2 Statistics

<table>
<thead>
<tr>
<th>Mann-Whitney U test</th>
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<tr>
<td>Early visual: Control (27 ± SD 3.11) vs Group 1 (67.8 ± SD 6.49)</td>
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<tr>
<td>Early visual: Control (27 ± SD 3.11) vs Group 2 (48.6 ± SD 8.2)</td>
<td>0.001</td>
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<tr>
<td>Early visual: Control (27 ± SD 3.11) vs Group 3 (35.8 ± SD 4.49)</td>
<td>0.003</td>
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<tr>
<td>Half-life: Control (129.2 ± SD 11.00) vs Group 1 (260.4 ± SD 18.99)</td>
<td>0.001</td>
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<tr>
<td>Half-life: Control (129.2 ± SD 11.00) vs Group 2 (224.6 ± SD 13.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>Half-life: Control (129.2 ± SD 11.00) vs Group 3 (189.2 ± SD 8.52)</td>
<td>0.001</td>
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</tbody>
</table>

Kruskal–Wallis test

| Early visual: Control vs Group1 vs Group 2 versus Group 3 | <0.001 |
| Half-life: Control vs Group 1 vs Group 2 vs Group 3 | <0.01 |
Group 3: 49 bubbles/mm², mean diameter = 112 μm (±SD 32) and mean wall thickness = 20 μm (±SD 6) (Figure 3).

Surface tension was 7.3 N/m for distilled water. Control group = 5.54 N/m. Group 1 = 5.45 N/m. Group 2 = 5.35 N/m. Group 3 = 5.21 N/m. Precision error ± 0.02 N/m.

Discussion

Foam sclerotherapy has shown to be a much more efficacious treatment than sclerotherapy with liquid agents. Dilution and efficacy loss of the liquid agent in veins with more than 4 mm of diameter are very quick. This makes the results difficult to predict. However, foam has a special rheological behaviour that increases contact time with the endothelium. When a foam flows along a tube, it behaves like a solid, i.e. it does not shift until a certain mechanical force or tension greater than its elasticity limit (‘yield stress’) is applied. Upon faster degradation, yield stress is reached before and the foam behaves like a liquid. Most surgeons use the Tessari technique and ambient air to obtain foam. It is easily obtained and safely administered. The problem with polidocanol foam and this formation method is that degradation is faster than intended, and the efficacy may be compromised if the delivery is not immediate.

Certain sclerosants, called detergents (polidocanol and sodium tetradecyl sulphate), have a special chemical characteristic. They are amphiphilic molecules, i.e. with a hydrophilic pole and a hydrophobic pole, with surfactant or tensoactive properties. When mixed with gases, they acquire a dispersed micellar arrangement, with bubbles separated by liquid film (lamella) of various thicknesses depending on the foam quality. Ideally, the lamella of bubbles are connected in threes at an angle of 120° at the connection point, known as Plateau Border.

The study of foam stability is particularly complex in its mathematical formulation. It includes factors such as the density and viscosity of the liquid, type of gas (more or less diffusible), chemical characteristics of the substances involved, especially surface tension and concentration, production temperature, pressure the foam is subjected to, manufacturing energy, etc.

Physical methods have been described to make polidocanol foam more stable, especially its production with high-pressure gases and, therefore, with more energy. They require some special, patented devices that make them less practical and have, therefore, failed to become very popular. Other methods, such as microfilters between both syringes, are based on an increased contact surface of the liquid–gas system, creating greater turbulence and foam with smaller and, therefore, more stable bubbles.

Our work hypothesis resulted from the study of foam stability in general, which is produced by three main factors: Van der Waals forces among molecules, the electrostatic effect created by surfactants and the Marangoni effect, which acts as a lamella-restorative force. For that, we considered the Marangoni effect (mass transfer along an interface between 2 fluids due to the surface tension gradient) and its formulation based on lamellar thickness (viscosity) and surfactant concentration:

\[ Mg = -\frac{d\sigma}{dT} \frac{1}{\eta \alpha} \times L \Delta T \]

where \( \sigma \) is the surface tension, \( \eta \) is viscosity, \( \alpha \) is thermal diffusivity, \( L \) is the characteristic lamellar thickness and \( T \) is temperature. In practical terms, the Van der Waals forces and the electrostatic effect are little modifiable to confer stability to foam. However, we are able to act on the surface tension and viscosity of polidocanol with a tensoactive agent.

Glycerin is atoxic, has tensoactive properties, is more viscous than polidocanol, and is also moisturizing. Empirically, we added small amounts of glycerin to polidocanol and proceeded to produce foam following the standard method. Previous mathematical studies led us to perform the trials with small amounts of glycerin at low concentrations.
The results of the time measurements undoubtedly indicate that small amounts of glycerin stabilize polidocanol foam. Besides, this simple chemical method is easily reproducible and applicable. Specifically, a 1.66% glycerin concentration in 3% polidocanol (Group 1) produces foam two times more stable than 3% polidocanol alone. Increased glycerin concentration in the mixture did not result in greater stability. They did maintain above baseline values, but in the 5% glycerin concentration (Group 3), the times of foam decay offered very little difference from the baseline measurements, although statistically significant.

In their paper on the influence of glycerin on sodium tetradezyl sulphate foam stability, Peterson and Goldman7 also predicted that there had to be a point where the glycerin stabilizing power would diminish. This is due to the critical micellar concentration, a phenomenon presented by surfactant or tensoactive agents by which, from a certain concentration of said agents, the foaming power is maximal. According to the Marangoni number formulation, a pure liquid does not produce stable foam. On the contrary, if the concentration of the tensoactive agent is too high, superficial layers will be almost exclusively made of the said agent, and foam formation will not be significant either. Thus, for each surfactant mixture there are some adequate concentrations to achieve maximum foam stability.

The bi-dimensional microscopic study of foam provides valuable information on this phenomenon. Factors affecting the breaking down of foam are gravity, which conditions fluid drainage towards the foam base; osmotic pressure, which produces continuous drainage from the lamella to Plateau Borders; and Laplace’s Law, which induces the formation of larger bubbles.12,14 The microscopic observation of the various concentrations shows a decreased number of bubbles with an increased thickness of lamellae and Plateau Borders, increasing the gravitational and osmotic effect (Figure 3).

In the accuracy measurements on the surface tension of mixtures, a progressive reduction of the surface tension values is observed with increasing glycerin concentrations. If we only took the surface tension factor into account, the foam obtained should be more stable, as we increased the glycerin concentration; however, this is not so. Gravitation and the osmotic effect counteract this reduction in surface tension observed as we add more glycerin. We speculate with that gas ratio must be modified at higher glycerin concentrations in order to provide more dry and stable foam.

Peterson and Goldman’s7 paper cited above speculates on the efficacy and distant side-effects of foam with a longer half-life. Our group has been using polidocanol foam with small amounts of glycerin on a regular basis for two years. Data are yet to be published, but we have not observed a high number of complications. We think that with foam being more stable, the pace of degradation is slower and the likelihood of producing complications from gases (ambient air) is lower, although this needs more investigation. It should be noted that the foam’s greater stability and, therefore, its greater efficacy have to be taken into account when choosing the polidocanol concentration. Each polidocanol concentration will require a different ideal addition of glycerin that has to be studied and experienced for each group. The future publication of the clinical results will provide the correct usefulness to more stable polidocanol foam.

Acknowledgements

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References