An Investigation on the Influence of Hyaluronic Acid on Polidocanol Foam Stability

An-Wei Chen, MD,* Yi-Ran Liu, MD,† Kai Li, MD,* and Shao-Hua Liu, MD, PhD*

BACKGROUND Foam sclerotherapy is an effective treatment strategy for varicose veins and venous malformations. Foam stability varies according to foam composition, volume, and injection technique.

OBJECTIVE To evaluate the stability of polidocanol (POL) foam with the addition of hyaluronic acid (HA).

MATERIALS AND METHODS Group A: 2 mL of 1% POL + 0 mL of 1% HA + 8 mL of air; Group B: 2 mL of 1% POL + 0.05 mL of 1% HA + 8 mL of air; Group C: 2 mL of 1% POL + 0.1 mL of 1% HA + 8 mL of air. Tessari's method was used for foam generation. The half-life, or the time for a volume of foam to be reduced to half of its original volume, was used to evaluate foam stability. Five recordings were made for each group.

RESULTS The half-life was 142.8 (±4.32) seconds for 1% POL without the addition of HA, 310.6 (±7.53) seconds with the addition of 0.05 mL of 1% HA, and 390.4 (±13.06) seconds with the addition of 0.1 mL of 1% HA.

CONCLUSION The stability of POL foam was highly increased by the addition of small amounts of HA.

The authors have indicated no significant interest with commercial supporters.

Foam sclerotherapy is an effective and commonly used treatment strategy for varicose veins and venous malformations.¹–³ Polidocanol (POL) is the most widely used sclerosant agent. Stability is one of the characteristics of sclerosant foams that determines their sclerosing power.⁴ Foam stability has been reported to be influenced by different gases, methods of preparation,⁵ the liquid air fraction,⁶ sclerosant concentration,⁷ and temperature.⁸ Viscosity is an important influential factor for the sclerosant foam stability.⁵ Some articles on the influence of the addition of glycerin to sclerosant agent—sodium tetradecyl sulphate and POL—have been recently published, the addition of glycerin to a sclerosant foam can prolong foam stability due to the increased viscosity of glycerin.⁹,¹⁰

Hyaluronic acid (HA) is an autologous substance that exists in the blood at a certain concentration.¹¹ Intravenous injection of 0.03 to 0.75 g/L concentrations of HA in humans was reported to be safe.¹²,¹³ Hyaluronic acid is a natural linear glycosaminoglycan that is biodegradable, nontoxic, and non-immunogenic¹⁴ and it is viscose. It is soluble in water and, therefore, absolutely chemically compatible with POL. We found that the POL foam stability was influenced by the addition of HA. Few studies have been performed on the POL foam influenced by the addition of HA.

The aim of this article was to describe POL foam stability variation based on its association with HA.

Materials and Methods

The materials included POL (1% lauromacrogol injection; Shanxi-Tianyu, Xian City, China); HA with...
a molecular weight of 150 to 250 kDa, non-
crosslinked, derived from bacteria (20 mg/2 mL Sofast
Sodium Hyaluronate Injection; Shandong Bausch-
fruida Pharmaceutical Co Ltd., Shandong, China); air
at room temperature; 10-mL silicone-free syringe
(WEGO, Weihai City, China); and 3-way tap (WEGO).

Tessari’s method\textsuperscript{15} was used to generate sclerosant
foam. Twenty passes were performed in the standard
way to obtain the foam. The new syringes and 3-way
taps were used for each test. Room temperature was
controlled at 22°C.

Three groups were studied in this experiment: Group
A: 2 mL of 1% POL + 0 mL of 1% HA + 8 mL of air;
Group B: 2 mL of 1% POL + 0.05 mL of 1% HA + 8
mL of air; Group C: 2 mL of 1% POL + 0.1 mL of 1%
HA + 8 mL of air.

The half-life, or the time for a volume of foam to be
reduced to half of its original volume (half-volume),
was used to evaluate foam stability like in other
works.\textsuperscript{7,8} When the foam filled the 10-mL syringe, the
syringe was disconnected from the 3-way tap and
placed exactly vertical with the rubber plug of the
syringe on the bottom. The timer was started. Over
the course of time, as the foam degenerated back into
its constituents, the sclerosant solution was found to
gradually reform at the bottom of the syringe. When
the bottom of the solution’s meniscus attained an
exact volume of 1.0 mL as measured by the scale on
the side of the syringe, the timer was stopped. The
time was recorded in seconds and the time was the
half-life. Five sets of duplicate half-lives in Group A,
Group B, and Group C were measured.

\textbf{Results}

After 5 sets of recordings were gathered for all 3
groups of the study, it was found that the half-life
was greater when HA was combined with POL. The
half-lives were 139 to 150 (mean 142.8 ± 4.32)
seconds for 1% POL without the addition of HA,
300 to 320 (mean 310.6 ± 7.53) seconds with the
addition of 0.05 mL of 1% HA, and 373 to 405
(mean 390.4 ± 13.06) seconds with the addition of
0.1 mL of 1% HA. These results are summarized in
Table 1.

\textbf{Discussion}

Liquid sclerosants have the disadvantage of being
diluted by the blood, resulting in an insufficient level of
the desired effect at the injection site. In contrast, foam
sclerosant displace the blood instead of mixing with it
and occupy the interior of blood vessels.\textsuperscript{16–18} Stability
is one of the characteristics of sclerosant foams that
determines their sclerosing power.\textsuperscript{4}

Foam stability has been reported to be influenced by
different gases and methods of preparation,\textsuperscript{5} the liquid
air fraction,\textsuperscript{6} and sclerosant concentration.\textsuperscript{7} Low
temperature can enhance the stability of POL foam.\textsuperscript{8}
Another agent that has been reported to enhance the
stability of POL foam is glycerin; the longest half-time
recorded for POL supplemented with glycerin was 280
seconds for 3% POL with 1.66% glycerin.\textsuperscript{10} In our
study, the addition of HA prolonged the POL foam
half-life by 173.38%.

Hyaluronic acid is a natural linear glycosaminoglycan
and is more viscous than POL. Hyaluronic acid alone

<table>
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<th>TABLE 1. Foam Half-Life Stability</th>
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<tr>
<td><strong>Group A</strong>: 2 mL of 1% POL + 0 mL of 1% HA + 8 mL of Air (Seconds)</td>
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<tr>
<td>143</td>
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<tr>
<td>139</td>
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<td>Mean = 142.8 ± 4.32</td>
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cannot be made into the foam with air; however, small amounts of it can enhance the stability of POL foam, although the mechanism behind this is unclear. We presumed that this effect is mostly due to enhancement of foam viscosity. Viscosity is an important influential factor on sclerosant foam stability; high viscosity enhances foam homogeneity and stability. It is reasonable to conclude that increased viscosity generated by the addition of HA strongly enhanced the stability of the foam.

In this study, our experimental data supported that the addition of HA could prolong the half-life of POL foam. We may speculate the prolonged half-life of POL/HA foam could result in a more efficacious sclerotherapy result due to a prolonged contact time of the foam bubbles with the endothelial cells. There also exist a potential that owing to prolonged foam half-life and slower pace of degradation, the occurrence of distant air embolism may be reduced. However, safety and efficacy studies in a clinical setting are necessary.

Conclusion

This study revealed that the stability of POL foam is highly increased by the addition of small amounts of HA.

References


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