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Improvement of stability of polidocanol foam for nonsurgical permanent contraception☆,☆☆

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Abstract

Background: Polidocanol foam (PF), used clinically as a venous sclerosant, has recently been studied as a safe and inexpensive means for permanent contraception. Delivering the sclerosant to the fallopian tubes as a foam rather than a liquid increases the surface areas and thus enhances the desired epithelial disrupting activity of the agent. However, the foam is inherently unstable and degrades with time. Therefore, increasing foam stability and thus duration of the agent exposure time could increase epithelial effect while allowing reduction in agent concentration and potential toxicity.
Materials and Methods: We studied methods to improve foam properties that might improve safety and efficacy of PF for intrauterine application. Several types of microporous filters adapted to a syringe-based foaming device were used to study the effect of pore structures on the formation of PF. The foam drainage time and bubble size were characterized. The addition of benzalkonium chloride (BZK) to polidocanol was also investigated for its effects on foam characteristics.
Results: A syringe-based foaming device adapted with an inline filter produced smaller bubble PF with a longer foam drainage time. PF generated with a circular pore filter lasts longer than with a noncircular pore filter. The addition of 0.01% of BZK also improved the stability of PF.
Conclusion: The stability of PF is affected by the pore characteristics of the filter used for foam generation and enhanced by the presence of a small amount of BZK. The improved foam, if shown to be efficacious in animal models of contraception, could lead to a safe, simple and inexpensive method alternative to surgical contraception.

Keywords: Tubal occlusion; Permanent contraception; Female; Polidocanol foam; Stability; Benzalkonium chloride

1. Introduction

Polidocanol is a nonionic surfactant that is used clinically for venous sclerotherapy. The activity of a surfactant-based sclerosant can be increased by delivering the agent as a foam. The rationale for using foam is to provide the greatest therapeutic effect while using the lowest total dose of the injected agent. A recent report demonstrating fallopian tubal occlusion in macaques following transcervical treatment with 5% polidocanol foam (PF) provides the basis for studying foam sclerotherapy as a novel and inexpensive alternative approach to surgical permanent contraception for women [1]. One advantage of adapting polidocanol for this use is that the compound is currently approved by the Food and Drug Administration (FDA) (0.5% and 1%) for use in venous sclerotherapy.

To ensure adequate epithelial damage and reliable tubal sclerosis, an optimal foam preparation must have sufficient stability to remain in contact with the target tissue for an adequate treatment interval. Liquid drainage and bubble coarsening, coalescence or rupture adversely affects foam stability during delivery before exposure to the epithelium in the fallopian tubes and leads to incomplete or inadequate treatment. The nonhuman primate studies of PF for permanent contraception have compensated for this problem by using a higher concentration (5%) of PF than is currently approved for human use [1]. Improving the stability of PF may increase polidocanol exposure time and PF delivery to the epithelial cells and thus allow use of lower concentrations for permanent contraception. A variety of approaches have

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been evaluated to improve foam stability for venous sclerotherapy; changing the foaming gas, adjusting polidocanol concentration, varying pH or temperature, adding chemicals and modifying the foaming device [2–6]. We explored two novel approaches to improve PF stability: (1) the effect of filter pore structure on foam formation (mechanical) and (2) the addition of a small amount of benzalkonium chloride (BZK) that has surfactant properties to stabilize bubbles (chemical).

2. Materials and methods

Polidocanol (Sigma-Aldrich P9641) and BZK (Sigma-Aldrich 234427) used in this study were both chemical grade. Three types of commercial 5-μm filters were evaluated in this study: polytetrafluoroethylene microporous membrane (Filter #1, Millipore LSWP01300), nylon mesh (Filter #2, Spectrum Laboratories 145814) and polycarbonate track-etched membrane (Filter #3, Millipore TMTP1300). The surface morphology of the three filters was characterized with scanning electron microscope (SEM) (FEI Quanta 200). The filters for SEM characterization were sputter coated with 20 Å of Au/Pd metal.

Four separate solutions (3% polidocanol, 5% polidocanol, 0.01% BZK and 0.1% BZK) were prepared by dissolving polidocanol or BZK in water and mixing overnight. Two polidocanol solutions containing 0.01% BZK and 0.1% BZK were prepared by adding BZK to 3% stock polidocanol solution and mixing overnight. A modified double-syringe technique originally described by Tessari [5] was used for foam preparation. Briefly, 2.4 mL of foaming solution and 9.6 mL of air (1:4 ratio) were mixed in two 12-mL syringes connected via a three-way stopcock with an inline filter holder by pushing the plungers back and forth 20 times to generate foam. Triplicate experiments were prepared for each type of filter and each concentration of polidocanol solution with and without BZK. Foams generated with 3% polidocanol without filters and without BZK were used as a control.

To estimate the foam bubble size, the freshly made foam was immediately sandwiched between two microscopic slides (3×2 inches) with a 30-μm spacer and microscopic images of the bubbles were taken with iPhone 5s camera equipped with a ProScope microscope (Bodelin Technologies, Oregon, USA). The diameter of the individual bubble was measured with ImageJ software [7] and the mean diameter of the bubbles at the image center (1.5×1.5 mm) was used for foam comparison.

To evaluate foam stability, the foam drainage was measured with a method similar to that used in prior studies of polidocanol and other foams [6,8]. Briefly, a total of 10 mL of freshly made foam was immediately dispensed into a 15-mL conical bottom graduated glass tube. Foam stability was assessed by measuring the time (in seconds) required for 1 mL of liquid to drain and accumulate from the foam (drainage time). The longer the drainage time is, the more stable the foam is.

All values were expressed as mean±standard deviation (n=3). One-way analysis of variance analysis with post hoc test was used to evaluate statistical significance; $p<.05$ was considered significant for each of the independent experiments.

3. Results

3.1. Effect of membrane filter on PF stability and bubble size

The SEM images of the top surfaces of Filters #1, #2 and #3 are shown in Fig. 1. The microscopic appearance of the pore structure showed marked differences between filters: Filter #1 pores were irregular and tortuous, Filter #2 had rectangle-like pores and Filter #3 pores were regular and circular.

Fig. 2 illustrates the comparison of mean drainage time for 3% PF generated without and with the various filters. Compared to no filter (mean drainage time of 184.67±5.13 s), the use of any filter (Filter #1, #2 or #3) significantly improved foam stability ($p<.05$). Further comparison among these three types of filters revealed that PF prepared using Filter #3 had a significantly longer drainage time (227.00±3.46 s) than foam prepared with Filter #1 (210.33±8.02 s, $p<.05$) or Filter #2 (215.00±4.36 s, $p<.05$) (Fig. 2).

Mean bubble diameter for 3% PF generated with and without a filter is shown in Fig. 2. Consistent with the results of the foam stability assay, PF generated without a filter resulted in a larger bubble size (107.06±6.31 μm) than filter-generated foam. Although all 3 filters have the same pore size (5 μm), the mean bubble diameters of PF prepared with the filters differed significantly (Fig. 3). Filter #3 produced significantly smaller bubbles (68.90±0.56 μm) than Filter #2 (74.33±3.41 μm, $p<.05$), and Filter #2 bubbles were significantly smaller than Filter #1 (87.63±6.37 μm, $p<.05$).

3.2. Effect of BZK on stability and bubble size of PF

Our initial observations of foaming behavior of low concentrations of BZK solutions without polidocanol showed that BZK foams were unstable. The drainage time of foam prepared with 0.1% BZK solution without polidocanol was less than 1 min and the foam prepared with 0.01% BZK solution without polidocanol collapsed immediately after it was formed (data not shown).

However, when BZK was added to 3% polidocanol solution, the resulting combined BZK/PF appeared more uniform and stable. Fig. 4 displays the drainage time observed for 3% PF with and without BZK and for 5% PF without BZK (the current standard) under the same foaming conditions including the same filter (Filter #3). The addition of 0.1% BZK to 3% PF significantly increased the drainage time (336±9.54 s) compared to 3% (227.00±3.46 s, $p<.05$) or 5% (274.67±0.57 s, $p<.05$) PF without BZK. Interestingly, a decrease of the BZK concentration from 0.1% to 0.01% did not result in a significant change in drainage time (336±9.54 s vs. 321.67±13.58 s, $p=.18$) for 3% PF.

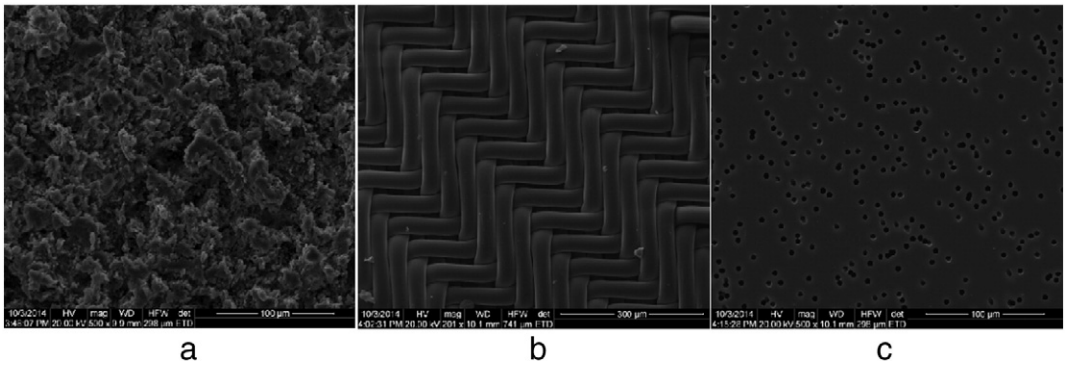

Fig. 1. SEM images of the top surface of (a) Filter #1, (b) Filter #2 and (c) Filter #3.

4. Discussion

A safe, simple and inexpensive approach to nonsurgical permanent contraception would improve family planning options for women who desire no further pregnancies. Although 1% PF is FDA approved for use as an agent for venous sclerotherapy, higher concentrations have been required to achieve sclerosis of the fallopian tubes in a nonhuman primate model [1]. Improvement of foam stability and lifetime could increase the exposure time and PF delivery to the epithelium during treatment and result in greater damage to the epithelium and underlying stromal tissue, leading to more reliable tubal occlusion. Strategies that optimize foam stability may make it possible to use of lower concentrations of polidocanol for nonsurgical permanent contraception. Although both 1% and 3% PF have been evaluated for venous sclerotherapy, no clinical benefit is seen with the higher concentration [3]. There is no clinical data on the safety of 5% PF so strategies that could improve the effectiveness of lower concentrations of polidocanol for use in permanent contraception should improve safety and acceptability of the approach. Our results demonstrate that a 5-μm filter improves the quality (stability and bubble size) of 3% PF and that the combination of a 5-μm filter and 0.01% BZK resulted in foam quality superior to that 5% PF.

Use of a 5-μm filter hub to generate foam with another detergent based surfactant, sodium tetradecyl sulfate, has previously been reported [9]. The novel finding in our study is that filter pore structure also influences foam performance. The circular pores (Filter #3) produced more stable foam than the other shapes tested. One possible explanation for this effect is that the regularity of pore shape (circular) produces bubbles of a highly regular shape during the initial generation and that these may be more stable than those produced by filters with irregular shaped openings. Further investigation of other types of filters with different pore characteristics is in progress.

BZK is a cationic surfactant with antimicrobial and antiviral activity. It has a long history of FDA allowance for a broad spectrum of medical uses and approved in topical treatments such as eye drop, wound and vaginal treatments.

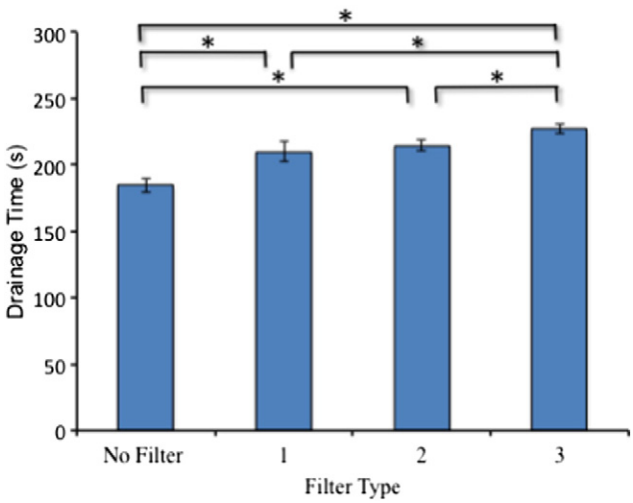

Fig. 2. The time required for 1 mL of liquid to drain and accumulate from 10 mL of PF (3% polidocanol) generated with three types of filters with different pore characteristics: tortuous (Filter #1), rectangle-like (Filter #2) and circular (Filter #3). Results are mean±STD (n=3), *p<.05.

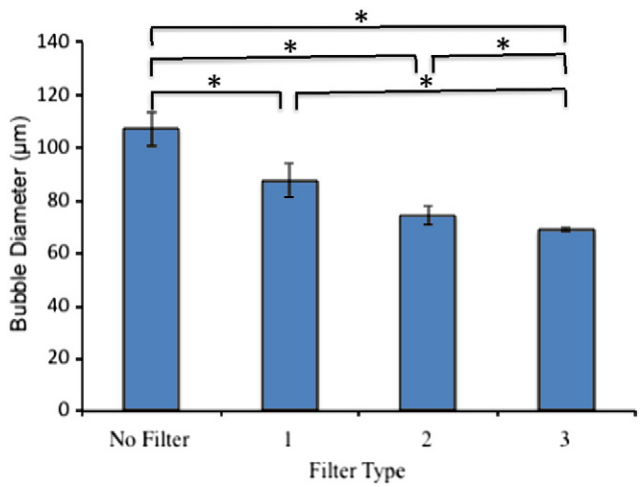

Fig. 3. Bubble diameter of PF (3% polidocanol) generated with three types of filters with different pore characteristics: tortuous (Filter #1), rectangle-like (Filter #2) and circular (Filter #3). Results are mean±STD (n=3), *p<.05.

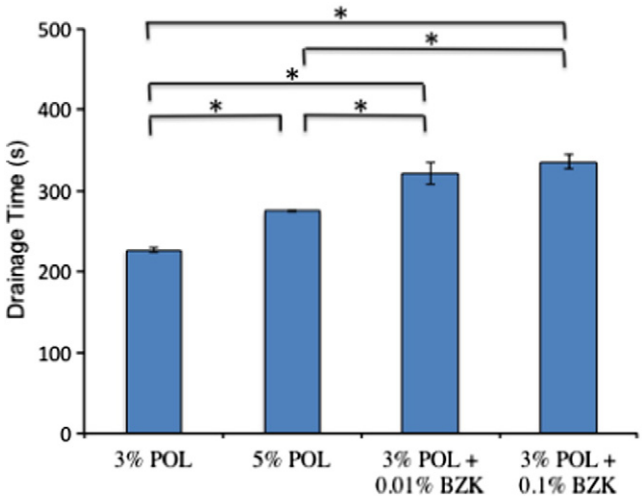

Fig. 4. The time required for 1 mL of liquid to drain from 10 mL of PF prepared with 3% polidocanol without and with BZK and 5% polidocanol without BZK. All PF were generated with Filter #3. Results are mean±STD (n=3), *p<.05.

Clinical safety for internal use has not been fully evaluated. The critical micelle concentration (CMC) of BZK is around 0.02% [10]. The CMC of a surfactant is the minimum concentration required for the solution to form micelles or foam in the presence of a gas. The improvement of PF stability by BZK at a concentration below its CMC suggests that BZK is acting as a foam stabilizer rather than a foaming agent. This improvement occurs with a small addition of BZK; no further change in bubble size was observed when the concentration of BZK added to 3% polidocanol was increased from 0.01% to 0.1% (Fig. 5). Mixed surfactant systems have been reported to exhibit improve foam stability, when compared to their individual components

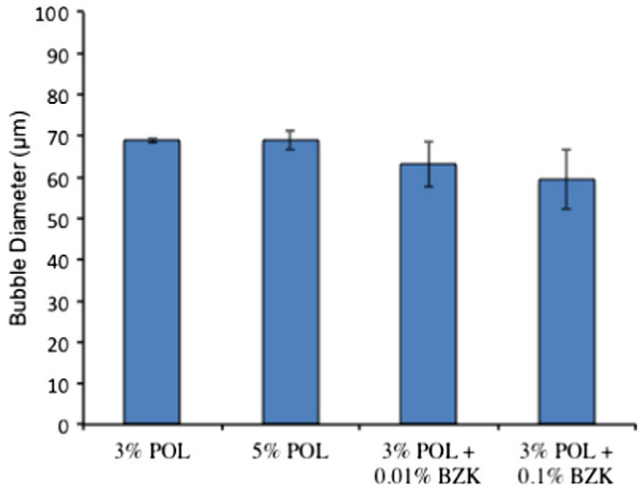

Fig. 5. Bubble diameter of PF prepared with 3% polidocanol without and with BZK and 5% polidocanol without BZK. All PF were generated with Filter #3. Results are mean±STD (n=3). There is no significant difference in bubble diameter between these PF.

[11,12]. In particular, mixtures at a molecular ratio of 1:3 or 3:1 lead to an interfacial phenomenon that results in more favorable hexagonal molecular arrangement (packing) that improves stability [13]. However, the molecular ratio of BZK to polidocanol used in the present study was much lower (<1:150). The observed stabilization of PF with this small amount of BZK may be in part due to a synergic effect, similar to that observed for a mixture of nonionic and cationic surfactants [14], although the mechanism is not fully understood.

Anatomically, major differences exist between veins and fallopian tubes with respect to the morphology and physiology. Unlike the endothelium of veins, the fallopian tube has a tortuous lumen with two types of epithelial cells (ciliated and secretory) filled with tubal fluid (secretions). The complexity of fallopian tube presents new challenges for the application of foam sclerotherapy. Currently, there is incomplete understanding of how PF interacts differently with this epithelium compared to endothelium, particularly in the presence of the tubular fluid instead of the blood. However, given the fact that the clinical evidence from the phlebology literature supports the superiority of foam over liquid polidocanol for larger veins, it makes sense to use foam for the purpose of nonsurgical permanent contraception [15]. The preliminary results from this study suggest that it may be possible to use low-cost physical and chemical approaches to increase the stability and activity of PF.

5. Conclusion

Preliminary results showed that the adaption of an inline filter in the syringe-based foaming device or the addition of small amount of BZK improved the stability of PF. The findings in this study provide a potential opportunity to reduce the concentration and dose of polidocanol required to produce tubal occlusion. The confirmation of these effects needs to be done in nonhuman primate models.

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