Background: Abnormal mucus composition and bacterial biofilms are thought to contribute to the pathophysiology of rhinosinusitis. Addition of a mucoactive surfactant to saline irrigation solution has been hypothesized to address these factors. We evaluated the safety and tolerability of a reformulated surfactant in a sample of normal subjects.

Methods: A total of 33 volunteers were randomly assigned to receive either surfactant solution or buffered saline at baseline in a controlled crossover study design. Each subject underwent rhinoscopic exam and in-office smell testing via the 40-question smell identification test (SIT). Those with non-normosmic results or active rhinitis symptoms were excluded. Subjects were instructed to irrigate twice daily with the selected solution for 1 week while keeping a daily diary. For week 2, treatment was stopped. During week 3, each group switched to the other treatment. Exam, SIT, and degree of congestion were assessed after each phase.

Results: Use of surfactant led to a marginal reduction in mean SIT score of 1.5 points, which was statistically significant ($p = 0.012$). A clinically meaningful reduction in SIT score, defined as $\geq 4$ points, was observed in 18% (6/33) of subjects after surfactant vs 3% (1/33) after saline ($p = 0.046$). During the surfactant phase, moderate or severe congestion was reported in 29% (8/28) of subjects completing the diary. In contrast, only 6% (2/32) of subjects reported moderate congestion after the saline phase ($p = 0.021$).

Conclusion: In normal volunteers, surfactant nasal irrigation may be associated with tolerability issues due to congestion. A subset may experience reduction in olfactory acuity that appears reversible. © 2017 ARS-AAOA, LLC.

Key Words: nasal irrigation; sinus irrigation; surfactant; olfaction; smell; congestion; smell identification testing


Nasal irrigation is a widely available and commonly practiced modality to manage sinonasal symptoms and specific disease processes such as chronic rhinosinusitis (CRS). Often the decision to utilize this therapy is initiated by the patient, particularly in situations when no prescription is required. Isotonic saline alone has been demonstrated to improve both the severity and frequency of sinonasal symptoms, particularly when delivered at low pressure and high volume.1 A hallmark of the modern era has included use of compounded prescription topical preparations containing antibiotics and/or corticosteroids for the topical management of CRS.2 In parallel, multiple nonprescription alternatives have been introduced for the management of sinonasal conditions including surfactants,3 oxidants, sugar alcohols (eg, xylitol),4 manuka honey,5 and colloidal silver.6 The spectrum of available irrigation options has been reviewed elsewhere.2 Surfactants have garnered particular attention given their potential to disrupt bacterial biofilms, which may play a prominent etiologic role in the development or persistence of CRS.3,7 Surfactants are molecules containing both hydrophilic and hydrophobic components, a property defining them as amphipathic. These substances are active at interfaces between liquids and solids or other liquids and have several important biomechanical properties including increasing the solubility of some substances, lowering surface tension, and decreasing friction between adjacent media. Biologically, in CRS, this may result in mucolytic8 and antimicrobial effects, with the latter occurring through disruption
Surfactants in common daily use include household soaps and detergents. Those that have been studied for use in CRS include a citric acid zwitterionic surfactant, diluted baby shampoo, and other proprietary soap-like irrigations developed specifically for sinonasal use, such as SinuSurf™ (NeilMed Pharmaceuticals, Santa Rosa, CA). These soap-like formulations have been investigated, both in vivo and in vitro. A solution of baby shampoo in buffered normal saline was found to inhibit (but not eradicate) pseudomonal biofilm at an optimal concentration of 1%. This was employed in a series of patients with recalcitrant CRS where subjective improvement was observed in approximately one-half of the patients. Three additional patients withdrew for tolerability issues. Among the 11 patients with pretreatment and posttreatment olfactory testing, 7 experienced improvement. Further studies by other authors demonstrated that this treatment modality was associated with significant prolongation of mucociliary clearance time (from 12.09 to 15.45 minutes) in healthy volunteers. SinuSurf is a proprietary surfactant product that has been demonstrated to induce a 3-log reduction in methicillin-resistant Staphylococcus aureus and a 6-log reduction in Pseudomonas aeruginosa when colony-forming units were assessed during in vitro studies. Furthermore, biofilm formation was reduced 83% and 76% for each of these organisms, respectively. In vitro studies using mucosal explants studied via scanning electron microscopy suggested that SinuSurf was associated with preservation of cellular architecture and ciliary ultrastructure. The present study was designed to investigate the safety and tolerability of a novel formulation of SinuSurf in healthy volunteers, with particular attention to subjects’ sense of congestion and olfactory acuity. It was hypothesized that adverse effects of this nature would be uncommon in healthy volunteers.

Subjects and methods

The study was designed as a single center, prospective, non-blinded, crossover trial of the tolerability and safety of a surfactant nasal irrigation solution (low-concentration SinuSurf) in normal subjects and was approved by the institutional review board of Vanderbilt University Medical Center. The primary quantitative outcome measure was change in the 40-item smell identification test score (SIT-40; Sensonics, Inc., Haddon Heights, NJ). Because there is no universally accepted value in the literature for a clinically significant change in SIT-40, the authors selected a value of ≥4. The study was designed to detect a change of at least 3 out of the 40 SIT items with ≥80% power and p ≤ 0.05 to assure changes of 4 or more would be identified validly. To meet these standards, assuming a 2-tailed hypothesis, 30 data points would be needed per group. It was anticipated this would be achieved by screening 40 healthy volunteers aged 18 to 65 years. Subjects were recruited using flyers placed around the medical center soliciting healthy volunteers. Subjects were compensated $25 plus parking for each office visit and were offered an additional $100 upon completion of the study. At the initial visit, each was evaluated by medical history, physical examination of the ears and nose, and the SIT-40. Exclusion criteria included any symptom or sign of active nasal or sinus disease, use of any nasal sprays, SIT-40 result that was not normosmic for age and gender, cystic fibrosis, immunosuppression from disease or therapy, history of previous endoscopic sinus surgery or nasal surgery, those not willing to use contraception or abstain from sexual relations during trial period, and any women who were concurrently pregnant. Qualified subjects were asked to return a week later to start the study period, at which time they were randomized. For the first week, one-half of the subjects received surfactant solution while the other one-half were given a buffered isotonic saline irrigation solution. Each treatment was conducted twice daily. The second week was a washout period where no irrigation was performed. During the third week, each volunteer was given the opposite irrigation solution, such that each subject served as his/her own control. Subjects were instructed on how to prepare and use each of the solutions according to the manufacturer’s instructions, and all materials (except the sterilized or distilled water) were provided. At each subsequent visit, subjects were asked to submit a symptom diary to assess congestion and epistaxis, graded as absent/mild/moderate/severe, and to provide additional comments. Each also underwent anterior rhinoscopy and otoscopy and were administered the SIT-40. The primary outcome measures were change in SIT-40 score from baseline, as assessed prior to each treatment phase, and degree of congestion at the conclusion of each treatment phase. The change in SIT-40 score was assessed by 2 methods before and after each treatment phase: (1) by absolute change from pretreatment baseline, and (2) according to the proportion of subjects who experienced a clinically significant reduction from baseline. As there is no established value in the literature for a minimal clinically significant change in SIT-40 score, this was defined as a change of ≥4 points based on clinical experience. Data was analyzed by paired t testing and chi-square, where appropriate and p ≤ 0.05 was considered statistically significant.

Results

Among the 40 screened volunteers, 33 met inclusion criteria (6 were not normosmic at screening and 1 was found to be over 65 years of age). This study group included 7 males and 26 females, with a mean age of 37.6 years. Race was reported as African American in 11, Asian in 1, and white in 21. Mean baseline SIT-40 score was 37.7 ± 1.5. Seventeen subjects were randomized to receive surfactant irrigations in the first phase, followed by saline, while the remaining 16 subjects were treated in the opposite sequence. All subjects completed the in-office study visits but diaries were returned incomplete in 5 subjects after the surfactant phase and 1 after the saline phase. No incidences of...
TABLE 1. Incidence of congestion*

<table>
<thead>
<tr>
<th>Phase</th>
<th>Completed diary (n)</th>
<th>Degree of congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>Surfactant</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Saline</td>
<td>32</td>
<td>30</td>
</tr>
</tbody>
</table>

*Moderate or severe congestion was more prevalent during the surfactant phase (p = 0.021).

TABLE 2. Change in SIT-40 score

<table>
<thead>
<tr>
<th>Phase</th>
<th>SIT-40 pretreatment (mean ± SD)</th>
<th>SIT-40 posttreatment (mean ± SD)</th>
<th>Change</th>
<th>Clinically significant reduction (≥4 n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant</td>
<td>37.6 (1.8)</td>
<td>36.1 (3.3)</td>
<td>−1.5 (3.3)*</td>
<td>6 (18%)**</td>
</tr>
<tr>
<td>Saline</td>
<td>36.9 (1.9)</td>
<td>36.9 (2.1)</td>
<td>0 (1.6)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

*p = 0.012 for change from pretreatment score.
**p = 0.046 for comparison between study arms.
SD = standard deviation; SIT-40 = 40-question smell identification test.

Epistaxis or need to stop treatment due to intolerance were observed during either surfactant or saline use. Volunteers were more likely to report treatment due to intolerance after the surfactant phase (Table 1). In this group, moderate or severe congestion was reported in 29% (8/28) of subjects completing the diary. In contrast, only 6% (2/32) of subjects reported moderate congestion during the saline phase (p = 0.021). Of the 8 subjects on surfactant rinses who developed significant congestion, 4 received the surfactant during the first treatment phase. In 2 of 4 of these individuals congestion was observed to resolve to none or mild during the subsequent washout and saline phases. In the other 2, congestion had resolved by 2 weeks after study conclusion in 1 subject and the other could not be contacted. These events were included in the analysis for a potential adverse outcome, noted below.

Mean pretreatment and posttreatment SIT-40 scores for each group are reported in Table 2. Saline use was not associated with changes in mean SIT-40 score, and 1 of 33 subjects (3%) experienced a change in score of ≥4 after the saline phase. This patient, coincidentally, reported no congestion. In contrast, a small but statistically significant mean reduction of SIT-40 score was observed following the surfactant phase (1.5 points, p = 0.012). Additionally, a decrease of ≥4 points was observed in 6 of 33 volunteers (18%) after surfactant use, which was significantly greater than was noted following saline (p = 0.046). Among these 6 subjects, declines of 4, 4, 5, 5, 8, and 15 points were observed, and 4 of these 6 volunteers also had congestion. The mean age of these patients was 41.5 years (31, 38, 42, 43, 47, and 48 years), which was nonsignificantly greater than that of the remainder of the sample (36.9 years, p = 0.35), and 5 of 6 were female. In 3 of these 6 subjects, the surfactant phase was completed first. These 3 volunteers thus had planned follow-up SIT-40 following the subsequent washout and saline phases, and smell was noted to recover to some degree in all 3 cases (Table 3). Two of the 3 volunteers who received surfactant during the last phase were successfully contacted for another follow-up SIT-40, done 2 and 3 weeks after finishing the study. Both of these individuals, (including the subject with a reduction of 15 points, had recovered to normosmia) (Table 4).

We calculated the proportion in each arm who had any potentially adverse outcome as the number of subjects, who at any time during the study period experienced any of the following: moderate/severe congestion, significant smell loss, or failure to complete the diary. This analysis was conducted presuming that those in the latter group may have neglected to do so secondary to dissatisfaction with the intervention. Using this methodology, rates of experiencing any potentially adverse outcome were 13 in 33 (39%) after surfactant use vs 4 in 33 (12%) following saline, and this did achieve statistical significance (p = 0.011).

**Discussion**

Detergent-like surfactants have demonstrated antimicrobial properties, both in vitro and in vivo. There is also evidence that addition of surfactant to saline improves distribution and penetration of the irritant. These potential advantages must be weighed against possible side effects that would impact compliance and quality of life. The present study was conducted to investigate potential tolerability issues of a novel proprietary formulation of SinuSurf®, comprised of buffered isotonic saline with the addition of glycereth-26, sorbitol, sodium lauryl sulfate, sodium lauryl sulfoacetate, disodium laureth...
sulfosuccinate, cocamidopropyl betaine, imidazolidinyl urea, tetrasodium ethylenediamine tetraacetic acid (EDTA) and United States Pharmacopeia (USP)-grade water. The final surfactant concentration was 25% that of an earlier, commercially available formulation. It was hypothesized that safety and tolerability, assessed by olfactory effects and patient-reported symptoms of congestion, would be acceptable in normal subjects. If that was found to be the case, these side effects may be inconsequential in CRS patients who commonly express symptoms of congestion and may manifest anosmia pursuant to the disease itself.

When compared to use of buffered isotonic saline, surfactant irrigations were associated with an increased prevalence of moderate or severe congestion and a clinically meaningful loss of olfactory acuity (at least 4 points on the SIT-40 test) in a greater proportion of healthy volunteers. It is likely that the observed impact on olfaction is attributable to the surfactant itself given that (1) the buffered salts were included during both phases of the study, and (2) others have demonstrated that saline rinses alone have no impact on either SIT score or cyclic adenosine monophosphate (cAMP), a potential biomarker of olfactory function. Other authors have reported that advancing age is associated with diminished recovery after olfactory insult. We observed a nonsignificant trend toward slightly older age in the 6 patients who experienced smell loss. Thus it remains possible, although unproven from this data, that age may have been a predisposing factor for such an outcome. It is notable, however, that smell function resolved to normosmic levels in 4 of 5 of the cases in which follow-up testing was available, while in the 5th case, recovery to within 2 points of baseline was seen. These findings suggest that, despite tolerability issues in normal volunteers, short-term (≤1 week) surfactant use was not associated with permanent significant loss of olfaction. This may have implications if patients elect to use an over the counter surfactant preparation for non-chronic conditions, such as a viral upper respiratory infection or to cleanse the nose after single exposures to irritants like dust or second hand smoke. Although in either phase of the study there were no instances of epistaxis or need to terminate treatment, the latter must be considered in light of the fact that subjects were compensated for participation. Additionally, when individuals who did not complete the diary were counted as treatment intolerant for statistical purposes, the rate of possible treatment side effects with surfactant was approximately 3 times that of saline use. This finding suggests patients should be counseled that surfactant therapy may have greater potential for side effects (including congestion and smell loss) compared to what they would have expected, or previously experienced, on saline rinses. Patients should also be made aware of possible risks of other commercially available homeopathic topical remedies for upper respiratory infections, including zinc gluconate, which has been implicated by some authors as damaging to nasal and olfactory mucosa.

Other potential limitations of the present study include a greater preponderance of females in the study group. However, when controlled for age, females generally manifest greater olfactory acuity and thus may be more sensitive to small change in smell. It should also be noted that the current study was conducted in healthy volunteers and was designed in this manner to assess treatment effects in a sample who would be most sensitive to changes in congestion or olfaction. Nonetheless, it remains unclear whether these findings would extend to the CRS population, but it is possible that the antimicrobial effects and symptomatic benefits in patients with biofilms or viscous mucus may outweigh potential surfactant-related side effects in patients who already manifest congestion and anosmia at baseline. This is a subject for future investigation.

Conclusion

In normal volunteers, surfactant nasal irrigation may be associated with tolerability issues due to congestion. A subset may experience reduction in olfactory acuity that appears to be reversible. Further investigations are necessary to determine factors that may predispose individuals towards experiencing these phenomena, and to what extent these outcomes may be experienced by CRS patients.

References
