

Safety of a Preservative-Free Acidified Saline Nasal Spray

A Randomized, Double-blind, Placebo-Controlled, Crossover Clinical Trial

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Objective: To determine the safety and tolerance of a buffered preservative-free acidified solution as an alternative to standard chemical preservatives to prevent microbial contamination of saline nasal spray.

Design: Randomized, double-blind, placebo-controlled, crossover clinical trial.

Setting: Tertiary academic medical center.

Participants: Healthy volunteers with no history or signs of sinonasal disease.

Interventions: Twenty volunteers used a buffered preservative-free acidified solution in a saline nasal spray and a benzalkonium chloride-containing saline nasal spray for 1 week each, separated by a 1-week washout period.

Main Outcome Measures: At study enrollment and after using each nasal spray solution, participants completed a visual analog scale symptom questionnaire and

the 20-Item Sino-Nasal Outcome Test and underwent nasal endoscopic examination, which was graded using a modified Lund-Kennedy scoring system. At the end of each test period, the contents of each nasal spray bottle were cultured for microorganism growth.

Results: All 20 participants completed the study. Four participants who developed upper respiratory tract illnesses during the study period were excluded from secondary analyses. No differences were observed in specific sinonasal symptoms or nasal endoscopy findings after use of either nasal spray. No nasal spray solutions from either group had any microorganism growth.

Conclusion: In a short-term study with a small sample size, a preservative-free acidified solution seems to be safe and well tolerated, while maintaining sterility in a multiple-dose applicator without use of chemical preservatives.

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THE HEALTH OF A TOPICAL nasal spray user relies on the prevention of contamination of the solution. Pharmaceutical manufacturers add various preservatives to destroy or inhibit the growth of microorganisms that may be introduced into the solution after the opening of its container. However, preservatives may cause local hypersensitivity or toxic effects at mucosal surfaces.

Benzalkonium chloride, the most widely used preservative, has been associated with sinonasal mucosal injury,¹⁻³ nasal squamous metaplasia,² ciliary dysmotility,^{4,5} genotoxicity,^{6,7} and other untoward adverse effects.⁸⁻¹⁰ Data also suggest toxic effects of phenylcarbinol, another common preservative.¹¹⁻¹³ Despite the evidence showing that benzalkonium chloride and other preservatives can be damaging to human and animal tissues,

preservatives are in widespread use in over-the-counter and prescription preparations. These agents have concentrations of preservatives at potentially toxic levels.⁶

Acidification to a pH of 2.5 offers an alternative method of maintaining sterility without use of chemical preservatives.¹⁴ We studied a novel saline solution formulation that is acidified by hydrochloric acid to a pH of approximately 2.5 and is buffered by low concentrations of citric acid.¹⁴

We completed a randomized, double-blind, placebo-controlled, crossover trial comparing a preservative-free acidified saline nasal spray (PFAS) with a commercially available benzalkonium chloride (and phenylcarbinol)-containing saline nasal spray (BAKS). Our objectives were (1) to determine the safety and tolerance of the PFAS and (2) to assess the antimicrobial effects of the PFAS when used in a multiple-dose container.

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STUDY DESIGN

The Stanford Institutional Review Board approved this study before enrollment of study participants. We obtained informed consent from each study participant in compliance with national patient privacy guidelines.

We recruited 20 healthy adult (≥ 18 years) study participants without a history of sinonasal disease. We excluded individuals with active or ongoing nasal or sinus symptoms due to environmental allergies, upper respiratory tract infections, or sinusitis. We excluded any participant with abnormal nasal endoscopy findings at the beginning of the study. We excluded any participants who were pregnant, participants who were unable to complete the questionnaire for whatever reason, and participants who were using any medications related to the treatment of sinonasal disease (eg, antihistamines, decongestants, and others).

A compounding pharmacy formulated the PFAS (Leiter's Rx Compounding, San Jose, California). The PFAS solution contains 0.9% sodium chloride and citric acid, with hydrochloric acid added to adjust the pH to 2.5. The pharmacist was responsible for ensuring that the solution was isotonic. We obtained the BAKS as an over-the-counter product at a local drugstore. The BAKS is an isotonic solution containing 0.65% sodium chloride, benzalkonium chloride, phenylcarbinol, disodium phosphate, and monosodium phosphate (Ocean Spray; Fleming Pharmaceuticals, Fenton, Missouri). Both solutions are isotonic, despite their difference in sodium chloride concentration.

The pharmacist placed equal amounts of the 2 test solutions in identical glass spray atomizer bottles that had equivalent standardized dispensing volumes. The pharmacist performed the randomization, thereby masking us, the study participants, nasal endoscopist, pathologist, and statistician to the identity of each nasal spray. We unmasked the data only after completion of the statistical analysis.

Study participants used one coded nasal spray bottle, with 5 sprays in each nostril twice a day for 7 days. This was followed by a 7-day washout period during which the participants did not use either of the nasal sprays. Participants then used the other coded nasal spray bottle, with 5 sprays in each nostril twice a day for 7 days. We gave the participants an instruction sheet to remind them of the dosing regimen. Participants signed an agreement to follow the dosing regimen exactly. One of us (W.R.R.) telephoned each participant during each 1-week period of nasal spray use to remind him or her to continue use of the nasal spray as instructed. Study participants were permitted to meet with us on the sixth or eighth day (in lieu of the seventh) if personal scheduling problems so required. At each follow-up visit, we confirmed in writing the participant's adherence to the regimen.

Participants completed 2 symptom questionnaires and underwent nasal endoscopy at the following 3 time points during the test period: on enrollment in the study, after 1 week's use of the first test bottle, and after 1 week's use of the second test bottle. To assess symptoms, we used an 8-symptom visual analog scale questionnaire and the 20-Item Sino-Nasal Outcome Test (SNOT-20).¹⁵ The visual analog scale assessed the following symptoms on a scale ranging from 0 (an absence of symptoms) to 10 (the highest degree of severity) points: nasal burning, smell disturbance, taste disturbance, nasal bleeding, purulent rhinorrhea, facial pain, headache, and sore throat. Participants were asked to rate the mean level of symptoms for the prior week. The SNOT-20 assessed 10 nasal-related and sinus-related symptoms and 10 psychological and behavioral symptoms on a scale ranging from 0 (an absence of symptoms) to 5

(the highest degree of severity) points. For statistical analysis, we used the total score and the nasal and sinus symptom subset score from the SNOT-20 questionnaire.

We scored the nasal endoscopic findings using a modification of the method by Lund-Kennedy,¹⁶ which scores the following signs from 0 to 2: polyps (0 indicates none; 1, middle meatus; and 2, beyond middle meatus), discharge (0, none; 1, clear and thin; and 2, thick and purulent), edema (0, absent; 1, mild; and 2, severe), scarring or adhesions (0, absent; 1, mild; and 2, severe), and crusting (0, absent; 1, mild; and 2, severe). We added a score for erythema (0 indicates absent; 1, mild; and 2, severe). For our analysis, we summed the scores for the right and left nasal cavities for each sign. Therefore, each sign had a possible score ranging from 0 (an absence of the abnormal sign) to 4 (the highest degree of severity, bilaterally). For each participant, we also calculated a total score for all 6 signs. The nasal endoscopist was unaware of the symptom questionnaire results at the time of scoring. Each participant received a \$20 coffee coupon card for completing the study.

At the end of each participant's weeklong trial of each nasal spray, we obtained a 1-mL aliquot sample from the bottle under sterile conditions and plated the aliquot on blood and chocolate agar culture media dishes. The agars underwent incubation at 37°C for 72 hours at Stanford Hospital Microbiology Laboratory (a Clinical Laboratory Improvement Act-certified laboratory), Stanford, California. A pathologist with microbiological certification (Niaz Banaei, MD, Clinical Microbiology Laboratory, Stanford University Medical Center), masked to the type of nasal spray used, then quantified the colonies of each of 40 sets of blood and chocolate agars for microorganism growth and identity.

STATISTICAL ANALYSIS

We performed statistical analyses using commercially available software (SAS statistical package, version 9.1; SAS Institute, Cary, North Carolina). We performed analyses on an intent-to-treat basis. The primary set of analyses included all 20 participants. A secondary set of analyses excluded 4 participants who developed an upper respiratory tract illness over the course of the study period. Adjusting for participant and period effects, we compared the 2 treatment groups' visual analog scale scores, SNOT-20 scores, and Lund-Kennedy nasal endoscopy scores by repeated-measures analysis of variance using the SAS procedure PROC GLM. Using residual plots, we examined assumptions of analysis of variance. We used bivariate χ^2 analysis or the Fisher exact test to compare frequencies of events between the 2 treatment groups. Because the sample size was small, we considered significance at the 0.10 and 0.05 levels.

RESULTS

Twenty asymptomatic participants with normal nasal endoscopy findings enrolled and completed the study. We excluded 3 initial participants who had abnormal results on nasal endoscopic examinations.

Three other study participants used their nasal spray 1 day less (6 days total) or 1 day more (8 days total) to accommodate meeting with us to complete the questionnaires and undergo nasal endoscopy. One study participant used the BAKS nasal spray 2 weeks instead of 1 week because she could not make the 1-week follow-up appointment for personal reasons. Another study participant had a 2-week washout period during which she

Table 1. Symptoms Among 16 Study Participants Without Upper Respiratory Tract Infection

Symptom	Participants With Symptom, No. (%)		P Value	Score, Mean (Range)		P Value
	Post-BAKS	Post-PFAS		Post-BAKS	Post-PFAS	
Visual analog scale						
Nasal burning	1 (6)	2 (13)	>.99	0.31 (0-5)	0.69 (0-6)	.40
Smell disturbance	1 (6)	0	>.99	0.06 (0-1)	0	.40
Taste disturbance	1 (6)	0	>.99	0.63 (0-10)	0	.40
Nasal bleeding	1 (6)	2 (13)	>.99	0.19 (0-3)	0.19 (0-2)	.95
Purulent rhinorrhea	0	1 (6)	>.99	0	0.13 (0-2)	.27
Facial pain	1 (6)	0	>.99	0.44 (0-7)	0	.40
Headache	4 (25)	1 (6)	.33	0.75 (0-5)	0.13 (0-2)	.06 ^a
Sore throat	3 (19)	1 (6)	.60	0.56 (0-5)	0.06 (0-1)	.12
SNOT-20						
Need to blow nose	4 (25)	4 (25)	>.99	0.25 (0-1)	0.25 (0-1)	>.99
Sneezing	3 (19)	4 (25)	>.99	0.19 (0-1)	0.25 (0-1)	.54
Runny nose	8 (50)	5 (31)	.47	0.56 (0-2)	0.38 (0-2)	.42
Cough	3 (19)	3 (19)	>.99	0.44 (0-3)	0.31 (0-2)	.56
Postnasal discharge	4 (25)	3 (19)	>.99	0.25 (0-1)	0.25 (0-2)	.86
Thick nasal discharge	1 (6)	2 (13)	>.99	0.06 (0-1)	0.13 (0-1)	.54
Ear fullness	1 (6)	1 (6)	>.99	0.06 (0-1)	0.13 (0-2)	.64
Dizziness	2 (13)	0	.48	0.25 (0-3)	0	.27
Ear pain	3 (19)	0	.23	0.31 (0-3)	0	.17
Facial pain or pressure	2 (13)	1 (6)	>.99	0.25 (0-3)	0.06 (0-1)	.45
Difficulty falling asleep	1 (6)	2 (13)	>.99	0.06 (0-1)	0.12 (0-1)	.41
Wake up at night	3 (19)	1 (6)	.60	0.31 (0-2)	0.06 (0-1)	.22
Lack of good night's sleep	5 (31)	5 (31)	>.99	0.75 (0-3)	0.56 (0-3)	.55
Wake up tired	6 (38)	5 (31)	>.99	0.63 (0-3)	0.56 (0-3)	.86
Fatigue	7 (44)	8 (50)	>.99	0.81 (0-3)	0.87 (0-3)	.69
Reduced productivity	2 (13)	3 (19)	.63	0.25 (0-3)	0.31 (0-3)	.40
Decreased concentration	3 (19)	3 (19)	>.99	0.25 (0-3)	0.31 (0-3)	.54
Frustrated, restless, irritable	6 (38)	3 (19)	.43	0.69 (0-2)	0.38 (0-3)	.12
Sad	3 (19)	3 (19)	>.99	0.38 (0-3)	0.43 (0-3)	.76
Embarrassed	2 (13)	2 (13)	>.99	0.19 (0-2)	0.31 (0-3)	.50
SNOT-20 nasal and sinus subset	12 (75) ^b	9 (56) ^c	.46	2.60 (0-8)	1.75 (0-9)	.42
SNOT-20 total	13 (81)	13 (81)	>.99	6.94 (0-30)	5.69 (0-27)	.49

Abbreviations: BAKS, benzalkonium chloride-containing saline; PFAS, preservative-free acidified saline; SNOT-20, 20-Item Sino-Nasal Outcome Test.

^a $P < .10$.

^bMean (range), 1.93 (0-7) symptoms.

^cMean (range), 1.43 (0-6) symptoms.

did not use nasal spray instead of a 1-week washout period because she could not make that follow-up appointment.

We excluded 4 of 20 study participants from the main results who developed an upper respiratory tract infection during 1 of the 2 treatment weeks. Two were using the BAKS and 2 were using the PFAS when they became ill.

The demographics of 16 study participants were as follows: a mean age of 36.3 years (age range, 24-65 years), 7 male and 9 female, and 10 white, 1 black, 4 Asian, and 1 Indian race/ethnicity (as determined by us).

At the initiation of the study, participants reported minimal, if any, sinonasal symptoms based on the questionnaire results. The mean visual analog scale score for each sinonasal symptom (nasal burning, smell disturbance, taste disturbance, nasal bleeding, purulent rhinorrhea, and facial pain) was 0. The mean visual analog scale score for headaches was 0.31 of 10. The mean visual analog scale score for sore throat was 0.0625 of 10. The pretreatment mean SNOT-20 score was 5.94 (range, 0-17) of 100.

Table 1 summarizes scores on the visual analog scale and SNOT-20 questionnaire for 16 study participants who reported no upper respiratory tract illness during the study period. The mean visual analog scale score for headache during the BAKS trial was 0.75 (range, 0-5), higher than the 0.13 (range, 0-2) during the PFAS trial ($P = .06$). Four of 16 participants (25%) in the BAKS trial reported headache vs 1 of 16 participants (6%) in the PFAS trial ($P = .33$). There were no other statistically significant differences between the 2 trials in the number of participants affected or in the mean scores for a specific symptom. There were no statistically significant differences in SNOT-20 scores between the pretreatment, post-BAKS, and post-PFAS groups.

Table 2 summarizes signs using the modified Lund-Kennedy scoring system for nasal endoscopy among 16 study participants. There were no statistically significant differences in nasal endoscopy scores between any of the treatment groups. Following use during the study, none of 40 nasal spray solutions had any microorganism growth in the blood or chocolate agar media.

Table 2. Nasal Endoscopic Signs Among 16 Study Participants Without Upper Respiratory Tract Infection

Sign ^a	Participants With Sign, No. (%)		P Value	Score, Mean (Range)		P Value
	Post-BAKS	Post-PFAS		Post-BAKS	Post-PFAS	
Polyp	0	0	...	0	0	...
Discharge	4 (25)	4 (25)	>.99	0.38 (0-2)	0.31 (0-2)	.54
Edema	3 (19)	1 (6)	.60	0.44 (0-4)	0.06 (0-1)	.27
Scarring or adhesions	0	0	...	0	0	...
Crusting	0	0	...	0	0	...
Erythema	7 (44)	7 (44)	>.99	0.88 (0-2)	0.69 (0-2)	.66
Total	10 (63) ^b	10 (63) ^c	>.99	0.95 (0-3)	0.75 (0-2)	.35

Abbreviations: BAKS, benzalkonium chloride-containing saline; ellipses, not applicable; PFAS, preservative-free acidified saline.

^aRight plus left sides.

^bMean (range), 0.88 (0-3) signs.

^cMean (range), 0.75 (0-2) signs.

COMMENT

This study compares the tolerance of saline nasal sprays containing the BAKS vs the PFAS. Using a randomized, double-blind, placebo-controlled, crossover study design, we found no major differences in symptoms or endoscopic findings after use of the BAKS vs the PFAS. Both were associated with few symptoms or signs after 1 week of use.

We analyzed the presence or absence of symptoms and the mean score for each symptom. That the range of possible scores was 0 to 10 for the visual analog scale and 0 to 5 for the SNOT-20 questionnaire enabled the participants to report subtle degrees of symptoms. Even so, headaches were the only symptom that increased after use of the BAKS. Although the visual analog scale scores for headache were statistically significantly different between the BAKS vs PFAS trials, the magnitude of headache was minor in both. Furthermore, headache is non-specific and may not necessarily be related to the sinonasal system. Even with the slight increase in the mean headache scores reported by the participants, headache would not be expected to be a significant adverse effect associated with use of the BAKS.

Of those analyzed, we believe that the most important symptoms for determining the safety and tolerance of the PFAS nasal spray are nasal burning, smell disturbance, taste disturbance, nasal bleeding, purulent rhinorrhea, sore throat, need to blow nose, sneezing, runny nose, postnasal discharge, thick nasal discharge, ear fullness, ear pain, and facial pain or pressure (both the visual analog scale and the SNOT-20 questionnaire examined facial pain). There were no discernible differences in these symptoms between the 2 nasal sprays used.

Of those analyzed, we think that the most important signs for determining the safety and tolerance of the PFAS nasal spray are discharge, edema, erythema, and the growth of polyps. We found no significant differences in these signs between the 2 nasal sprays tested.

We conclude that use of the BAKS or PFAS can cause some degree of tolerable sinonasal symptoms or signs (Tables 1 and 2) but that the magnitude of these effects is small. The PFAS seems to be comparable to the BAKS in safety and tolerance.

Furthermore, the PFAS seems to have effective anti-septic properties similar to those of the BAKS in maintaining comparable sterility of the stored solutions. Other forms of contamination prevention such as refrigeration, pressurized aerosol containers, and single-dose containers have drawbacks. Refrigeration of liquid medications has the shortcomings of poor portability and the need for specialized storage for the manufacturer and for the consumer. Pressurized aerosol containers, which do not need preservatives because neither air nor microbes can enter as doses are extracted, are bulky and expensive for the manufacturer and for the consumer. Similarly, single-dose containers, which have the same advantage of requiring no preservatives, are cumbersome and costly.

In addition to providing a broad antimicrobial effect, low pH supports drug stability and longer shelf life for some commonly used nasal spray medications. For example, oxymetazoline hydrochloride and mometasone furoate are most stable at pH 2.5.^{17,18} There is also some evidence that acidity in saline may inhibit virus replication.¹⁹

The few participants in this study may have been insufficient to confirm differences in effects of the 2 nasal sprays. Furthermore, longer-term use of either nasal spray (>1 week) may have resulted in the development of more or increased symptoms or signs.

Four participants developed an upper respiratory tract illness that introduced symptoms and signs to the study that would confound the assessment of those due to the ingredients in the nasal sprays. We tried to mitigate this source of bias by dropping the participants from our secondary analyses. There seemed to be no stronger tendency to develop an upper respiratory tract illness with the BAKS vs the PFAS. Performing this study during summer months could have lessened the likelihood of upper respiratory tract illnesses among our participants.

In conclusion, the PFAS nasal spray used in this study seems to be safe, well tolerated, and effective at maintaining a sterile solution in a multidose applicator among a small sample of users over a short period. A larger series with longer follow-up is planned. Further studies are also necessary to explore use of a PFAS as a medium for drug delivery.

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Author Contributions: Dr Ryan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Ryan and Hwang. *Acquisition of data:* Ryan and Hwang. *Analysis and interpretation of data:* Ryan and Hwang. *Drafting of the manuscript:* Ryan and Hwang. *Critical revision of the manuscript for important intellectual content:* Ryan and Hwang. *Statistical analysis:* Ryan. *Obtained funding:* Hwang. *Administrative, technical, and material support:* Ryan and Hwang. *Study supervision:* Hwang.

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