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Xylitol Nasal Irrigation in the Management of Chronic Rhinosinusitis: A Pilot Study

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Objectives/Hypothesis: To determine the tolerability of xylitol mixed with water as a nasal irrigant and to evaluate whether xylitol nasal irrigation results in symptomatic improvement of subjects with chronic rhinosinusitis.

Study Design: A prospective, randomized, double-blinded, controlled crossover pilot study.

Methods: Twenty subjects were instructed to perform sequential 10-day courses of daily xylitol and saline irrigations in a randomized fashion, with a 3-day washout irrigation rest period at the start of each treatment arm. Collected data included patient characteristics, along with Sino-Nasal Outcome Test 20 (SNOT-20) and Visual Analog Scale (VAS) scores reported at the beginning and end of each irrigation course.

Results: Fifteen of the 20 subjects (75%) returned their SNOT-20 and VAS data for analysis. There was a significant reduction in SNOT-20 score during the xylitol phase of irrigation (mean drop of 2.43 points) as compared to the saline phase (mean increase of 3.93 points), indicating improved sinonasal symptoms ($P = .0437$). There was no difference in VAS scores. No patient stopped performing the irrigations owing to intolerance of the xylitol, although its sweet taste was not preferred by three subjects (21%). One patient reported transient stinging with xylitol.

Conclusions: Xylitol in water is a well-tolerated agent for sinonasal irrigation. In the short term, xylitol irrigations result in greater improvement of symptoms of chronic rhinosinusitis as compared to saline irrigation.

Key Words: Xylitol, saline, chronic rhinosinusitis, nasal irrigation, SNOT-20.

Level of Evidence: 1b.

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INTRODUCTION

Xylitol is a five-carbon sugar alcohol that has gained relative prominence in the past decade as a naturally occurring antibacterial agent. It is generally not believed to possess its own antibacterial properties; rather it appears to enhance the body's own innate bactericidal mechanisms.[1,2]

Based on these findings, we sought to explore the therapeutic potential of xylitol irrigations in treating chronic rhinosinusitis, a condition that has been estimated to affect nearly 14% of the population, with significant associated quality-of-life impairment.[3,4] Saline irrigation, which has been shown to be beneficial for patients with rhinosinusitis,[5] served as an accepted standard treatment for comparison. We conducted a prospective, randomized, crossover study to compare the therapeutic value of saline versus xylitol irrigations in patients with chronic rhinosinusitis.

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MATERIALS AND METHODS

Study Design

This study was a prospective, randomized, double-blinded, controlled crossover pilot study. Recruitment was done through a tertiary sinus specialty clinic, with all subjects enrolled between April and May 2010.

Before commencement of this study, institutional review board approval was obtained for the protocol, and all patients gave their written informed consent.

Patients

Eligible subjects were adults with chronic rhinosinusitis who had undergone bilateral endoscopic sinus surgery to include at a minimum maxillary antrostomy and anterior ethmoidectomy. Sinus patency was confirmed endoscopically to ensure adequate exposure to the irrigation solutions. Subjects were excluded if they had a history of immunocompromise, cystic fibrosis (CF), primary ciliary dyskinesia, active smoking, treatment with antifungal medications, an active bacterial infection requiring antibiotics, history of head and neck irradiation, active pregnancy, or granulomatous disease. Subjects who were taking other ancillary sinus medications, such as nasal steroids and antihistamines, were eligible as long as they maintained regular use throughout the study period.

Materials

Xylitol. Pharmaceutical-grade xylitol (Acros Organics, Fair Lawn, NJ) was premeasured and packaged in the hospital pharmacy into unlabeled, sealed packets each containing 12 mg of the sugar. Subjects were given 10 of these packets and instructed to dissolve the contents of one packet in 240 mL of

water (5% wt/vol) in a sinus irrigation bottle, followed by bilateral sinus irrigation once daily. They were instructed to use one packet daily for 10 days total.

Saline. Standard buffered isotonic individual-use salt packets (NeilMed, Santa Rosa, CA) were repackaged into unlabeled, sealed packets to maintain blinding. Each subject was given 10 of these packets as well and instructed to dissolve the contents into sinus irrigation bottles with 240 mL of water, with subsequent bilateral irrigation. One packet was to be used daily for 10 days.

The unlabeled packets of the xylitol and saline were placed respectively into two separate coded envelopes. Each subject was instructed to begin the trial with 3 days of no irrigation to allow for an initial washout period from any prior saline irrigation use. Then they were instructed to perform 10 days of once-daily irrigations with the first envelope's irrigants, followed by another 3-day washout period, and ending with 10 days of once-daily irrigation with the other irrigant. The order of irrigation was randomized using a random-number generator in a double-blinded fashion. Each subject was also given a prepaid, addressed envelope in which to return their outcomes surveys by mail at the conclusion of the study.

Outcomes Measures

Sino-Nasal Outcome Test 20. The Sino-Nasal Outcome Test 20 (SNOT-20) was given to all subjects to be completed at home on the first and final day of each irrigation course as the primary outcome measure. The test has a maximum score of 100 points based on the responses to 20 items.

Visual Analog Scale. Also given to all subjects at enrollment for their self-completion on the first and final days of each irrigation course, a single Visual Analog Scale (VAS) was collected as a secondary outcome survey. It was measured as a mark made by the subject on a 100-mm line to represent their overall sinonasal well-being, where the lowest extreme of the line (0) indicates the "worst" possible feeling, and the highest extreme end (10) represents "best" possible feeling. The mark was made in response to the question of "how you think your nose/sinuses are feeling overall."

Statistical Analysis

SAS Enterprise Guide 4.2 (SAS, Cary, NC) was used for data analysis. The differences between pre- and posttreatment SNOT-20 and VAS scores were compared between the two treatments for all collected data, utilizing a mixed-effects model. This method was also used to evaluate the effects of different treatment orders.

RESULTS

During the recruitment period, 23 subjects were screened and met criteria for inclusion in this study. Three subjects who met the inclusion criteria declined enrollment. Twenty subjects were recruited after providing their informed consent and signing appropriate institutional review board documentation.

Although all subjects served as their own controls, comparison of their demographics when grouped by sequence of treatment (saline then xylitol vs xylitol then saline) showed generally good matching. There were 10 subjects in each group. The average age was 44 years in both groups. The male-to-female ratio of the saline then xylitol group was 3:7; it was 7:3 in the other group. Nine (90%) in each group used nasal steroids. Five (50%) of the saline then xylitol group subjects also regularly took antihistamines, and two (20%) of the xylitol then saline group subjects used these medications. Data were not returned from three subjects in the saline then xylitol group and from two subjects in the other group.

Comparison of the pretreatment SNOT-20 scores between the xylitol and saline groups in the first round, as well as their comparison in the second round of the study, demonstrated no significant differences between their baseline values using a Student t test ($P > .05$). The mixed effects model also showed no significant difference based on sequence of treatment.

Fifteen (75%) of the subjects returned data for use in the analysis. One of these subjects completed only the first course of irrigant, withdrawing at that time because of complaints of a sore throat, but still providing pre- and posttreatment data for that first course. Of the five subjects who did not return data sheets, two (10%) withdrew from the study after enrollment because of time concerns, without starting any of the irrigations. Two (10%) subjects could not be reached by telephone for discussion or questioning about any issues with the study instructions. One (5%) subject started the first treatment arm but withdrew after 2 days, before completing the next data survey, because of an acute bacterial sinusitis that was treated with antibiotics. We were notified about this occurrence several weeks after she had stopped the irrigations.

The patient who withdrew during the first irrigation course because of an acute bacterial sinusitis had been irrigating with saline. The patient who withdrew after completing the first course of irrigations thinking it was causing a sore throat had been also using saline.

Utilizing the data collected from the 15 subjects on an intent-to-treat basis, the mean change in summated SNOT-20 score from pre- to postirrigation was an increase of 3.93 points for the saline irrigations, from 15 to 18.93. The mean change in total SNOT-20 score from pre- to postirrigation was down 2.43 points for the xylitol irrigations, from 17.93 to 15.5. This difference in treatment effect was statistically significant ($P = .0437$). (Fig. 1). There was no significant effect of the order of irrigation with saline or xylitol ($P = .27$). Of the subjects who completed both phases of irrigation ($n = 14$), comparing each participant's SNOT-20 scores to himself, nine had greater reduction of symptoms during the xylitol rinse phase versus the saline phase. Three subjects had greater reduction of symptoms with saline. Two subjects had no difference between the irrigation courses. (Fig. 2). For an as-treated analysis, excluding the one subject who only completed the saline irrigation but did not begin the xylitol irrigation, the difference in SNOT-20 scores was still significantly more improved for the xylitol irrigations ($P = .049$).

Using the same model to evaluate changes in the visual analog scale, the mean change for the saline irrigation from pre- to posttreatment was a drop of 0.07 from 6.85 to 6.78, whereas the corresponding change for the xylitol irrigation was an increase of 0.56 from 6.91 to 7.47. There was no statistically significant difference in

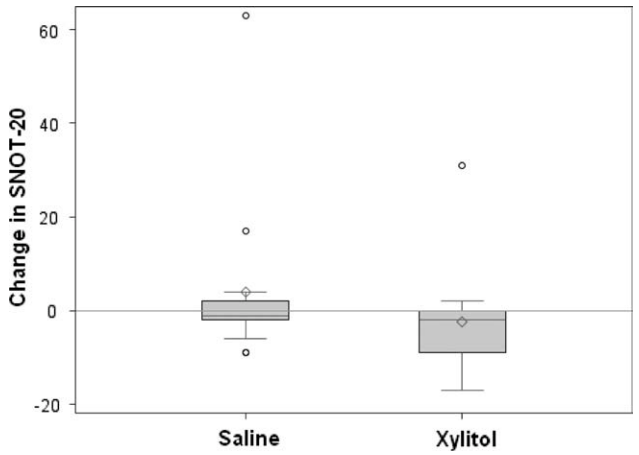

Fig. 1. Sino-Nasal Outcome Test 20 (SNOT-20) score change measured as SNOT-20 Final minus SNOT-20 Initial, for the respective irrigant. The distribution of saline scores hovers tightly around 0, whereas the distribution for xylitol is more notably in the negative region. Their difference was significant ($P = .0437$).

these treatments ($P = .35$) or their order ($P = .80$) (Fig. 3).

Based on some comments made by a few subjects on their data sheets, the sweet taste of xylitol hinted at the true identities of the blinded rinses; three subjects (21%) made such comments on their data sheets. Two subjects (14%) made negative comments regarding tolerance of the xylitol irrigant, ultimately stating "I do not like this [xylitol] irrigation" and "I have a tendency to gag during [the xylitol] rinse." Despite their negative comments, these two subjects still had more improvement during their xylitol rinses as compared to saline according to the SNOT-20 score changes. One subject (7%) reported minor stinging in his nose with the xylitol that went away quickly the first time and did not recur. Three subjects (21%) made negative comments about the saline rinses. There were no reports of stinging with the saline rinses.

Regarding overall safety, there were no adverse events noted after irrigating with the xylitol. Patients in the senior author's rhinology practice routinely contact our office when they develop acute sinusitis, and no subjects in this study called in with this problem during or within 2 weeks after completing the xylitol irrigations. There were, as discussed, two subjects who developed illness—one an acute sinusitis and the other an ostensible viral upper respiratory infection—during or shortly after performing saline irrigations, although a certain number of subjects would be expected to have such developments regardless of treatment, and we do not believe the saline had any causative role. Both of these subjects started the study with saline, and neither reached the xylitol portion.

DISCUSSION

Support for the therapeutic role of xylitol in chronic rhinosinusitis comes from basic science research on the airway surface liquid (ASL). The ASL, which coats the apical surface of airway epithelia, is known to contain multiple innate antimicrobial agents such as lactoferrin and lysozyme, among others, which function to combat the persistent influx of microbes on the surface of the airway.[1,6] Studies have shown that in respiratory epithelium affected by inflammation, irritation, and CF, the ASL chloride concentration is higher than normal.[6–8] In laboratory settings, the antibacterial properties of normal ASL diminish with increasing chloride

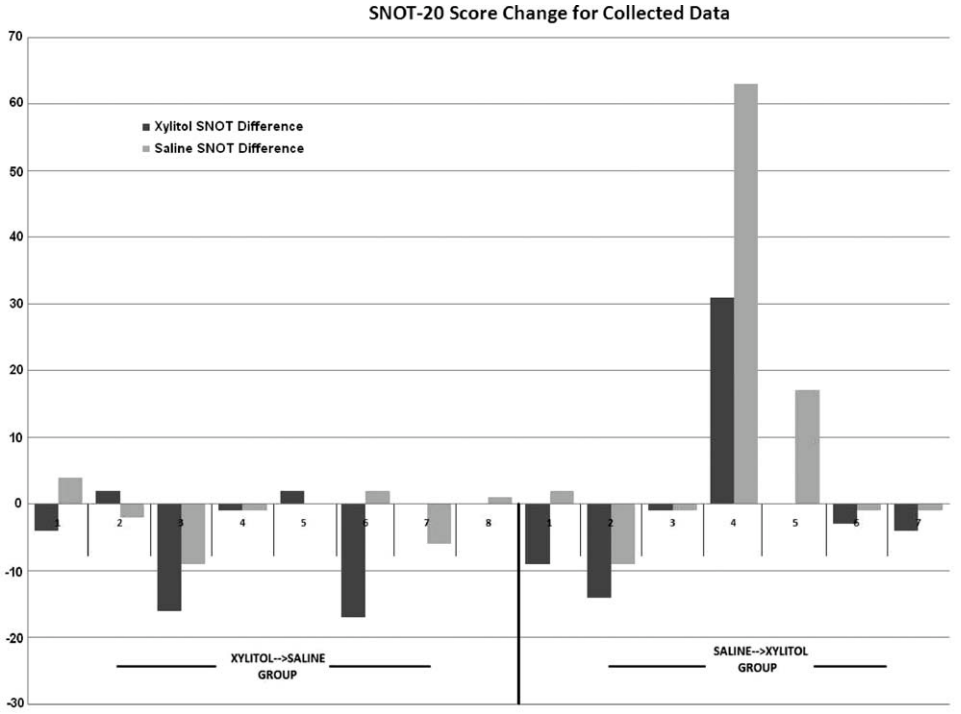

Fig. 2. Sino-Nasal Outcome Test 20 (SNOT-20) score change measured as SNOT-20 Final minus SNOT-20 Initial, for the respective irrigant. The omitted subjects are those who did not return any data. Subject 5 in the saline then xylitol group is the individual who withdrew after completing the first course of irrigation thinking it caused a sore throat.

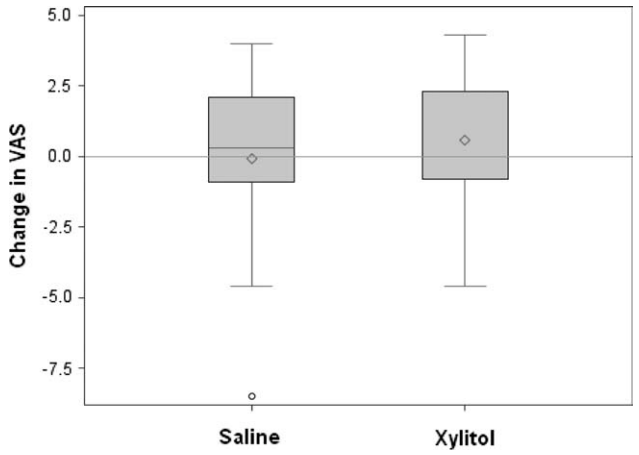

Fig. 3. Visual Analog Scale (VAS) change measured as VAS Final minus VAS Initial, for the respective irrigant. The distributions are similar for both irrigants. Although both trended toward showing improvement, the difference between them was not significant ($P > .05$).

concentrations, whereas conversely, CF tissue ASL demonstrates normalization of antibacterial properties simply by reducing the high salt concentrations with dilute saline.[6] These properties have been demonstrated using inoculates of *Pseudomonas*, methicillin-resistant *Staphylococcus aureus*, and *Escherichia coli*.

A study by Zabner et al.[1] investigated the potential of xylitol as an ideal solute for use on the ASL. They demonstrated that although xylitol will slowly diffuse across respiratory epithelia over several hours, a significant amount is able to stay on the apical surface and hold liquid solvent there as an osmolyte. When xylitol is applied to CF respiratory epithelia, it is also able to lower the ASL chloride concentration to values seen in normal samples. Importantly, common airway colonizing pathogens in CF, which include *P aeruginosa*, *S aureus*, coagulase-negative *Staphylococcus*, and *S saprophyticus*, were shown to be unable to utilize the xylitol for growth.

In a randomized, double-blind, crossover study,[1] subjects were randomized to either saline spray or a xylitol/water 5% wt/vol spray for 4 days, followed by a 1-week recovery period and then treatment with the other spray. *Staphylococcus* cultures were then compared pre- and posttreatment. Xylitol reduced colony counts by a median change of 500 colony-forming units (cfu) versus a 99 cfu reduction with the saline, which was judged significant ($P = .05$). None of the subjects reported adverse reactions to the xylitol. Similarly, an animal study[2] has also shown that simultaneous treatment of the New Zealand white rabbit maxillary sinus with 5% wt/vol xylitol and inoculum of *P aeruginosa* results in significant reduction in bacterial recovery versus saline.

More recent literature suggests that xylitol may act to destroy or damage biofilms. When 500 compounds were screened against *S aureus* biofilms under scanning electron microscopy, xylitol was one of two compounds identified as being active against the biofilm.[9,10]

Although most of the basic literature on xylitol has developed in the past 10 to 15 years, the clinical use of xylitol long precedes it, with studies being published as early as the 1970s reporting its inhibitory effects on dental caries when chewed in gum.[11] It is commonly thought that this result is secondary to effects on the biofilms of many dental pathogens.

The primary purpose of this pilot study was to evaluate the tolerability of xylitol as an irrigant when mixed with water in 5% wt/vol, the composition which has been previously researched in vitro and as a nasal mist spray.[1,2,12–14] There are no studies to our knowledge examining water-based xylitol used for full nasal irrigations. It was uncertain how this mixture would be tolerated by subjects without the buffering agents present in standard saline irrigations, the addition of which would have altered the osmolarity of our experimental irrigations. The data collected show that 5% xylitol in water is overall well-tolerated. Only one subject reported transient stinging, which resolved as he continued to irrigate with xylitol. Two subjects made negative comments about the xylitol, but both had better SNOT-20 score changes during their xylitol irrigation period. Three subjects made negative comments about the saline irrigations as well.

Although there was a statistically significant difference in the SNOT-20 scores between the xylitol and saline irrigation courses, with improvement being seen in the xylitol group and worsening seen in the saline group, the magnitude of score change is small with a mean 2.43 total point drop during xylitol irrigation and a 3.93-point increase during saline irrigations. This does not meet the 0.8-point individual item SNOT-20 change that represents clinically meaningful change, as determined by Piccirillo et al. in their validation study.[15] Also, we cannot explain why there was an increase in SNOT-20 scoring during the course of saline irrigation, as previous studies have demonstrated improvement, hence decrement, in SNOT-20 scores for patients treated with such irrigations for chronic sinusitis.[5]

There are a few limitations of this study that merit discussion. Although our best efforts were made to blind subjects to the treatments, three (21%) made note of the sweet taste associated with the xylitol and likely knew which treatment was which. One subject incorrectly guessed he was using xylitol during a course of saline irrigation. It is possible that more, if not the majority, of the subjects may have guessed or suspected which irrigant was xylitol without recording these observations, as all subjects were told as part of the informed consent process that the experimental agent was a sugar compound. They were not told about the potential for a sugary aftertaste, but we could not ethically obtain informed consent without disclosing the sugar-based nature of xylitol. If performed properly, however, the sweet aftertaste can be quite subtle in the opinion of the first author (J.D.W.). Nonetheless, knowledge of the identities of the irrigants may have biased the results.

The sample size of the study was also relatively small, although we were still able to obtain significant data with it. It was important to obtain pilot data demonstrating tolerance before investing more resources into a larger, longer study based on power calculations.

Recruiting 20 subjects and expecting a withdrawal rate of approximately 25%, we were pleased with our overall compliance rate of 75% (15 subjects).

Our withdrawal rate of five subjects (5 of 20, 25%) is essentially within our expected range but does confound the results. Although we are aware that two of them dropped out without even starting the study and one dropped out in the middle of the first course of irrigation owing to apparent acute infection (beginning with the saline irrigations and withdrawing before completing it), we do not have any such information from the final two subjects who did not return their data sheets.

Treatment times for the xylitol and saline were also short—10 days each. This decision again reflects concerns that longer course of treatment with water-based xylitol irrigations would not be well tolerated, potentially leading to noncompliance and withdrawals. Longer treatment periods in future studies may clarify the true magnitudes of potential differences in outcomes.

Also, most patients in this study were relatively asymptomatic, with lower-than-usual SNOT-20 scores. This observation is likely secondary to the fact that they had all undergone surgical intervention and could not, by formulation of study exclusion criteria, have had an acute bacterial sinusitis at the time of evaluation. Had more of our subjects had higher SNOT-20 scores at baseline, it may have been possible to see greater changes in symptoms. In addition, we asked our subjects to comply with a 3-day washout period before beginning each irrigant to minimize any residual effect bias. Ideally this washout period would have been slightly longer. This length was selected for two reasons: to minimize potential dropout during a prolonged period of inactivity within the study and to allay subject concerns regarding forgoing nasal irrigations for an extended period of time. All subjects except one were performing daily saline irrigations at the commencement of the study, with many expressing some anxiety about the 3-day hiatus.

CONCLUSION

Xylitol is a safe, natural five-carbon sugar that is gaining interest in many fields for promising data showing efficacy against chronic bacterial infections. We have shown that it is a well-tolerated sinonasal irrigant when mixed with water in a 5% wt/vol formulation, with only a few complaints regarding its inherently sweet taste and one isolated report of transient stinging. In our small, randomized, double-blinded controlled pilot, there were small but significant improvements in SNOT-20 scores with xylitol irrigation as compared to saline irrigation. Further studies with longer treatment courses and more subjects are merited to further delineate these findings and to determine their clinical significance.

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