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# Xylitol nasal irrigation in the treatment of chronic rhinosinusitis

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ABSTRACT

*Objective:* To evaluate the efficacy of xylitol nasal irrigation (XNI) treatment on chronic rhinosinusitis (CRS) and to investigate the effect of XNI on nasal nitric oxide (NO) and inducible nitric oxide synthase (iNOS) mRNA in maxillary sinus.

*Materials and methods:* Patients with CRS were enrolled and symptoms were assessed by Visual Analog Scale (VAS) and Sino-Nasal Outcome Test 22 (SNOT-22). Nasal NO and iNOS mRNA in the right maxillary sinus were also examined. Then, they were treated with XNI (XNI group) or saline nasal irrigation (SNI, SNI group) for 30 days, after which their symptoms were reassessed using VAS and SNOT-22, and nasal NO and iNOS mRNA in the right maxillary sinus were also reexamined.

*Results:* Twenty-five out of 30 patients completed this study. The scores of VAS and SNOT-22 were all reduced significantly after XNI treatment, but not after SNI. The concentrations of nasal NO and iNOS mRNA in the right maxillary sinus were increased significantly in XNI group. However, significant changes were not found after SNI treatment. Furthermore, there were statistical differences in the assessments of VAS and SNOT-22 and the contents of nasal NO and iNOS mRNA in the right maxillary sinus between two groups.

*Conclusions:* XNI results in greater improvement of symptoms of CRS and greater enhancement of nasal NO and iNOS mRNA in maxillary sinus as compared to SNI.



## 1. Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease involving the nasal and paranasal sinus mucosa. It is defined as chronic inflammation when it lasts longer than 3 months without complete symptom resolution. CRS is a common health problem which significantly affects quality of life. The disease has been estimated to affect 12.5% to 15.5% of the total population in the United States and 10.9% in Europe [1,2]. Saline irrigation has been shown to be beneficial for patients with CRS [3].

Xylitol is a five-carbon sugar alcohol that has gained extensive attentions in the past decades as a natural antibacterial agent. It decreases the salt concentration of human airway surface liquid that contains many antimicrobial substances, which can contribute to the improvement of the innate immune system, and thereby prevent airway infections [4,5]. In addition, this agent can exert antibacterial actions through disrupting glucose cell-wall transport and intracellular glycolysis, thus inhibiting bacterial growth [6]. An elegant study reported that xylitol nasal irrigation (XNI) could improve symptoms of CRS clinically [7]. However, the study did not evaluate the inflammatory conditions of the paranasal sinuses of those patients.

It is well known that nitric oxide (NO) provide a first-line defense via its antiviral and antibacterial action and via its upregulation of ciliary motility [8]. High concentrations of NO are found in normal paranasal sinuses, and the lack of NO may lead to the pathogenesis of sinus inflammation [9]. The epithelial cells in the paranasal sinuses were identified as the major source of NO in some studies, and inducible nitric oxide synthase (iNOS) would account for most of this NO production [10,11]. Measurement of nasal NO may be a useful tool in the diagnosis, management and assessment of patients with CRS [12].

A previous study demonstrated that xylitol at 5% stimulated NO production from macrophage, which inhibited macrophage infection by Leishmania amazonensis [13]. Macrophage is involved in chronic inflammation of paranasal sinuses though generating NO and cytokines [14,15]. Therefore, it is reasonable to hypothesize that xylitol treatment may control the development of CRS through regulating the NO concentration produced by macrophage or other cells located in sinus mucosa. Based on the above findings, we sought to explore the therapeutic potential of XNI in treating CRS and the influence of XNI on the inflammatory conditions of paranasal sinuses.

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## 2. Materials and methods

### 2.1. Study design

This study was designed as a prospective, randomized, double-blinded, controlled pilot study. Recruitment was done in the department of Otorhinolaryngology-Head and Neck Surgery, Huashan Hospital of Fudan University, with all patients enrolled between April and July 2016.

### 2.2. Study population

Thirty patients with CRS, aged between 35 and 67 years, had undergone bilateral functional endoscopic sinus surgery including at least maxillary antrostomy and anterior ethmoidectomy. Maxillary and ethmoid sinus patency was confirmed endoscopically to ensure adequate exposure to the irrigation solutions. Subjects were excluded if they had a history of allergic rhinitis, asthma, immunocompromise, cystic fibrosis, primary ciliary dyskinesia, active bacterial or fungal infection requiring antibiotics or antifungal medications, history of head and neck irradiation, current smoking, pregnancy, or granulomatous disease.

### 2.3. Study protocol

There were two study visits. At the first visit, patients underwent the evaluations that included clinical history, nasal endoscopy, Visual Analog Scale (VAS) and Sino-Nasal Outcome Test 22 (SNOT-22). Then, a 30-day treatment regimen was assigned in accordance with an independently generated random code to one of the following groups: xylitol (Acros Organics, Fair Lawn, NJ, USA) was premeasured and packaged in our hospital pharmacy into unlabeled, sealed packets each containing 12 g of the sugar. Participants were given 30 of these packets, and instructed to dissolve the contents of one packet in 240 mL of water (5% wt/vol) in a nasal irrigation bottle (Qiangjian medical instrument Co., Ltd., Yangzhou, China). Then, they were instructed to perform nasal irrigation (37 °C) bilaterally once daily and to use one packet daily for 30 days (xylitol nasal irrigation group, XNI group). Fresh solution was prepared for every use. Standard buffered isotonic salt packets (Nasal Rinse Mix, Qiangjian medical instrument Co., Ltd., Yangzhou, China) were packaged into unlabeled, sealed packets to maintain blinding. Each patient was given 30 of these packets and instructed to dissolve the contents in 240 mL of water in the nasal irrigation bottle. Then, they were instructed to perform nasal irrigation (37 °C) bilaterally once daily and to use one packet daily for 30 days (saline nasal irrigation group, SNI group). Also, fresh solution was prepared for every application. The technique of nasal irrigation was shown in Fig. 1A and B. At the second visit (after 30-day treatment), the scores of VAS and SNOT-22 were reassessed. During the whole study period, patients were instructed not to use any other drugs for the treatment of CRS.

### 2.4. Measurement of nasal NO

Nasal NO measurement was performed according to published procedures [13]. Patients had to refrain from eating and drinking at least for 1 h before the measurement. The procedures were performed using the NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). The nasal air was obtained directly from one nostril using the intrinsic flow of the electroluminescence analyzer with a target airflow rate of 0.25 L/min (aspiration/insufflation flows of ~5 mL/s). The probe was connected to a polystyrene nasal olive and gently inserted into the vestibulum of one nostril. The contralateral nostril was left open. To avoid contamination by NO originated from the lower airway, the patient was required to exhale orally against a resistance in order to close the soft palate. A nasal NO plateau showed steady state after ~20 s. The level of nasal NO was recorded.

### 2.5. Assessment of iNOS mRNA in the right maxillary sinus

Samples of mucosa in the right maxillary sinus of patients were taken endoscopically using a cup forceps device with local anesthesia and were frozen at −70 °C for mRNA extraction. Total RNA of samples was extracted with Trizol (Invitrogen, Carlsbad, CA) and treated with RNase-free DNase. For reverse transcription, 2 μg of the previously mentioned RNA was reversely transcribed with random hexamers (Invitrogen, Carlsbad, CA), and complementary DNA (cDNA) was amplified according to the manufacturer's instructions. Primers were designed using Primer Express Software (Applied Biosystems, Foster City, CA) from sequence available in GenBank and were synthesized (Geneland Biotech, Shanghai, China). Real-time reverse transcription polymerase chain reaction (RT-PCR) was performed to detect the mRNA of iNOS. iNOS primers were forward primer 5′-TGGATGCAACC CCATTGTC-3′ and reverse primer 5′-CCCGCTGCCCCAGTTT-3′. Glyceraldehyde-3-phosphate dehydrogenase mRNA was also examined to control the sample-to-sample variation in RNA isolation and integrity by using a pair of primers: forward primer 5′-ACCACAGTCCATGCCATCA C-3′ and reverse primer 5′-TCCACCACCCTGTTGCTGTA-3′. After initial denaturation at 95 °C for 10 min, the amplification profile was 15 s of denaturation at 95 °C and 1 min of annealing and extension at 60 °C

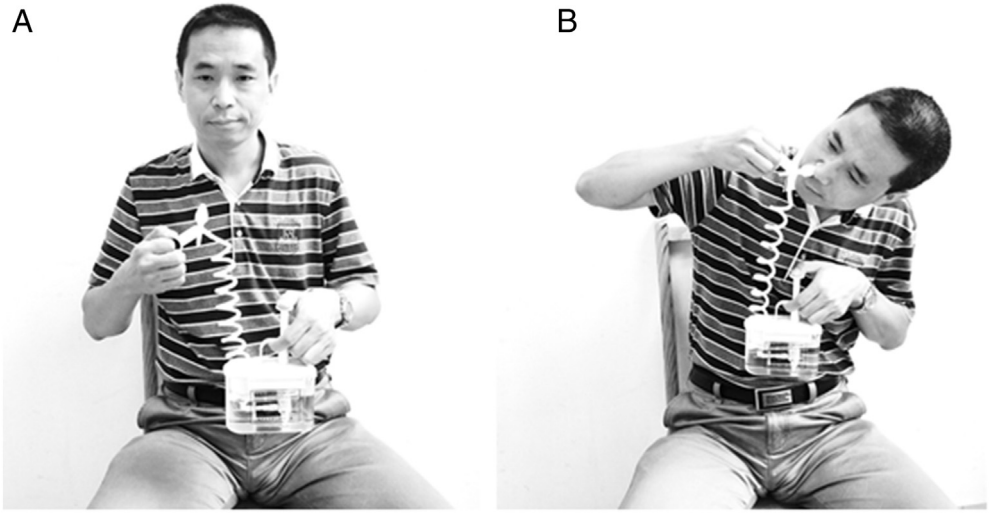


**Fig. 1.** Nasal irrigation technique. A, preparation. B, irrigation.

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for 45 cycles. Negative control RT reaction mixtures contained no reverse transcriptase and no cDNA in the PCR amplification mixtures. For measurement, 2 μL of diluted cDNA was amplified in a total reaction volume of 20 μL by using a 7500 real-time PCR System (Applied Biosystems, Foster City, CA) with 20× SYBR Green mixture (Invitrogen). Specificity of PCR products was evaluated by melting curve analysis and by size in agarose gels. Using 3 dilutions of cDNA, linearity of PCR amplification was controlled. Evaluation of data was performed using the cycle threshold (ΔCT) method with glyceraldehyde-3-phosphate dehydrogenase as internal standard.

### 2.6. Adverse effects

There were no adverse effects during the study period whether in XNI group or in NSI group.

### 2.7. Ethical considerations

The study was approved by the Ethics Committee of Huashan Hospital of Fudan University (no. 2014-249), and written informed consent was obtained from all participants.

### 2.8. Statistical analysis

The sample size was determined based on the reduction of the score of SNOT-22 in a previous pilot study, which suggested that 13 subjects per group would be required to detect a 2.4 difference in the SNOT-22 score reduction with an error of 0.05 (two tailed) and overall power (1-$\beta$) of 90%. Considering a loss of 10% of patients at follow-up, we recruited 15 participants in each study group. Statistical analysis was performed using a commercially available statistical software prism 6.0 (GraphPad Software Inc., San Diego, Calif., USA). The significance of changes within groups was assessed using the paired Student's *t*-test, and changes between groups were assessed using the Mann-Whitney *U* test. Data were expressed as means ± SEMs. $p < 0.05$ were considered to be statistically significant.

## 3. Results

### 3.1. Patient clinical characteristics and demographics

Of thirty patients, only twenty-five finished the study. Four subjects were excluded for poor adherence to treatment, and one did not complete the study for other reasons (Fig. 2). Demographic and clinical characteristics were similar between the two groups at baseline (Table 1), and there were no statistical differences in gender and age between them (Fig. 3A and B).

### 3.2. Comparisons of XNI and SNI group before treatments

The scores of VAS (Fig. 3C) and SNOT-22 (Fig. 3D), and the concentrations of nasal NO (Fig. 3E) and iNOS mRNA in the right maxillary sinus (Fig. 3F) before treatments were not statistically different between XNI and SNI group.

### 3.3. Effects of XNI treatment on CRS

There was a significant decrease after XNI treatment whether in the VAS (Fig. 4A) or in the SNOT-22 score (Fig. 4B). As for nasal NO and iNOS mRNA in the right maxillary sinus, the present study showed statistical increases of them after XNI intervention (Fig. 4C and D).

### 3.4. Effects of SNI treatment on CRS

For the treatment of SNI, we found there was no clinically significant decrease in the VAS (Fig. 5A) and SNOT-22 score (Fig. 5B). Furthermore, the study demonstrated that the concentrations of nasal NO and iNOS mRNA in the right maxillary sinus were also not enhanced significantly by the SNI treatment (Fig. 5C and D).

### 3.5. Comparisons of XNI and SNI treatment on CRS

To further verify which had better efficacies on CRS, we compared the scores of VAS and SNOT-22 between these two treatments. The study indicated that there were statistical differences between them,

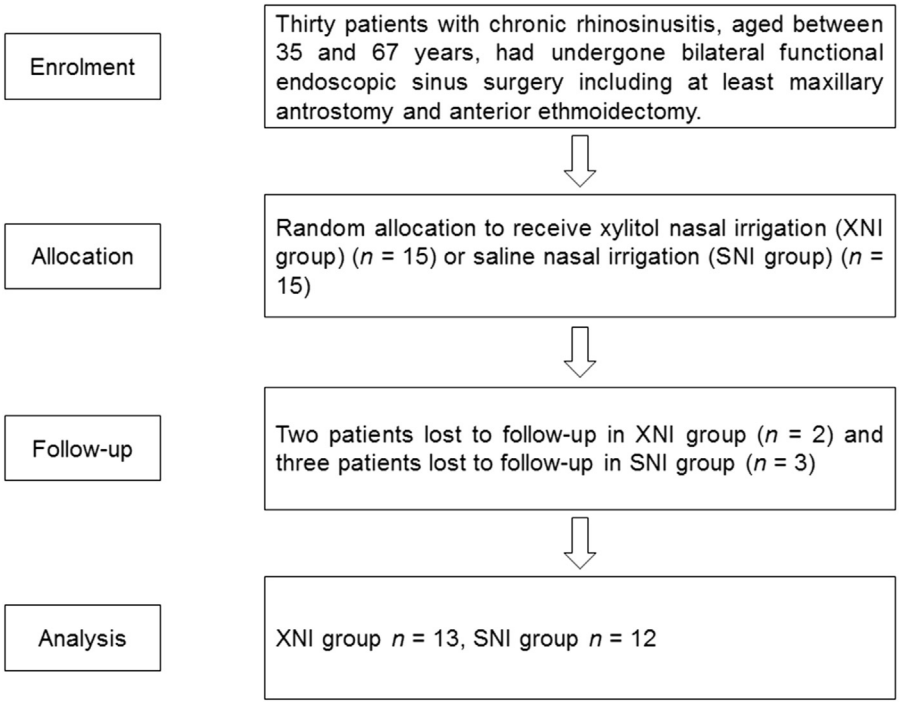


**Fig. 2.** CONSORT flow diagram.

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**Table 1**
Demographic and clinical characteristics the patients (n = 30).

| Patient characteristics | XNI group | SNI group |
|---|---|---|
| Total no. of patients | 15 | 15 |
| Age (mean years ± SEM) | 50.9 ± 2.3 | 50.1 ± 2.1 |
| Sex (male/female) | 7/8 | 9/6 |
| No. of patients withdrawn | 2 | 3 |
| Adverse effects | 0 | 0 |

XNI = xylitol nasal irrigation. SNI = saline nasal irrigation.

and XNI reduced these scores more than that after SNI (Fig. 6A and B), furthermore, XNI treatment increased significantly nasal NO and iNOS mRNA in the right maxillary sinus in comparison to those with SNI treatment (Fig. 6C and D).

## 4. Discussion

This study was designed as a randomized blinded controlled trial, furthermore, there were no statistical differences in gender, age, the scores of VAS and SNOT-22 and the concentrations of nasal NO and iNOS mRNA in the right maxillary sinus before treatments between XNI and SNI group. All of the above reduced potential bias.

On the basis of research on the airway surface liquid located on the surface of upper and lower airway epithelium which can inhibit microbial infection dependent on innate antimicrobial agents such as lysozyme, lactoferrin, human β defensins and cathelicidin LL-37 in the secretions [16], xylitol has been used in ear, nose and throat practice because of its role in the decrease of the salt concentration of the above liquid [17]. Furthermore, the agent inhibits the growth of *Streptococcus pneumoniae* in the presence of glucose, and also provides anti-adhesive effects on both *Streptococcus pneumoniae* and *Haemophilus influenzae* [18,19]. These micro-organisms are most likely to cause CRS in human [20]. Recent studies have suggested that xylitol may act to destroy *Staphylococcus aureus* biofilms [21,22] which often contribute to refractory CRS [20]. Additionally, an experimental study indicated that xylitol reduced induced sinusitis when administered simultaneously with bacteria in rabbit maxillary sinus [23]. Therefore, it is reasonable to think that we can use this sugar to treat CRS through its capability of enhancement of the body's own innate bactericidal mechanisms and suppression of growth of pathogenic bacteria. In 2011, a pilot study that was to evaluate the tolerability of xylitol as an irritant when mixed with water in 5% wt/vol demonstrated that xylitol in water was a well-tolerated agent for sinonasal irrigation [7]. But the study did not present an evaluation of the inflammatory conditions of the sinuses.

Based on the above investigations, we performed this study to evaluate 5% xylitol in water nasal irrigation treatment for CRS. As shown in the study, there were no statistical differences between two groups in the pre-treatment characteristics of patients including gender, age, the relevant scores of VAS and SNOT-22. After 30-day intervention, the outcomes suggested that treating CRS with XNI contributed to the improvements of VAS and SNOT-22 score, consistent with another study [7], however, there was no statistical differences in the assessments of VAS and SNOT-22 in SNI group, which was inconsistent with other previous studies [24,25] The reason for the ineffectiveness of normal saline irrigation on CRS might be that the sample size was too small or the duration of investigation was too short or others. We will carry out relevant studies further. In addition, XNI treatment reduced the VAS and SNOT-22 score more when compared to SNI. These findings indicated that 5% xylitol solution could improve the symptoms of CRS clinically.

More and more studies demonstrate that nasal NO levels in patients with CRS are significantly lower than those in normal subjects, which implies that NO possibly acts as an important mediator of innate mucosal defense mechanisms against sinus infection [9,26]. Measurement of nasal NO has become a useful tool in the assessment of CRS patients [12]. The epithelium located in the paranasal sinuses is the major source of NO, and will produce a large amount of NO production after its synthetase iNOS expression [10,11]. On the basis of these previous researches, we examined the concentrations of nasal NO and iNOS mRNA in the right maxillary sinus of patients to further evaluate the efficacy of XNI treatment on CRS.

The present study showed that treatment of CRS with XNI led to the significant increases of nasal NO and iNOS mRNA in the right maxillary sinus. But there were no statistical differences in the assessments of them in SNI group. Furthermore, the levels of nasal NO and iNOS mRNA in the right maxillary sinus in XNI group were increased more than those in SNI group. The result suggested that xylitol might promote the repairs of epithelial cells in the paranasal sinuses of CRS patients through inhibiting bacterial infections of sinuses. The inhibitory effects may be the results of the decrease of the salt concentration of sinuses surface liquid or/and the direct interfering of growth of bacteria existing

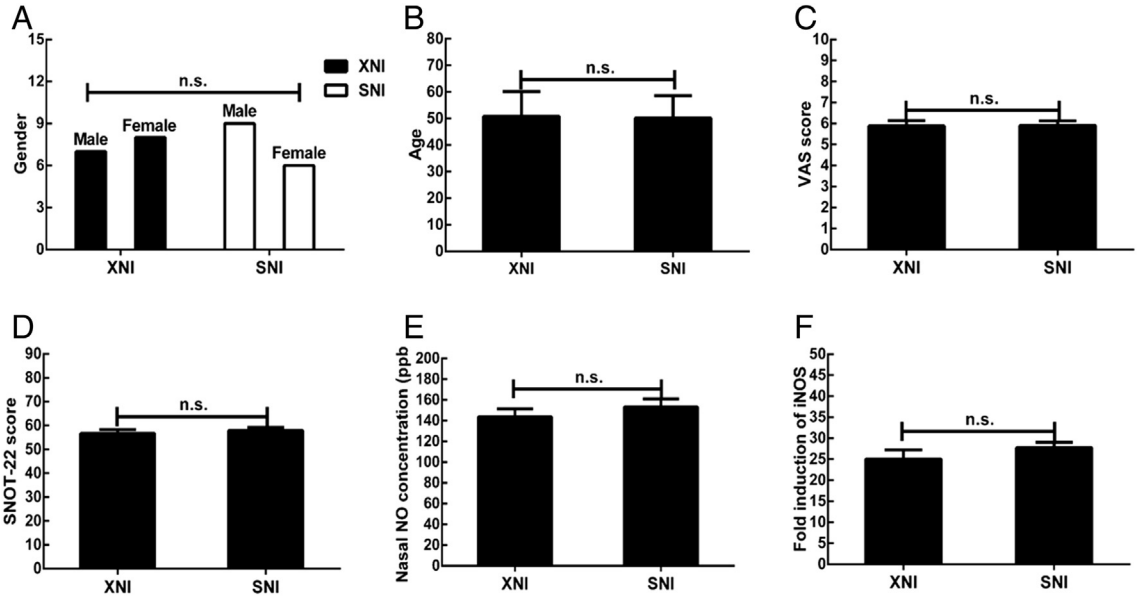


**Fig. 3.** Differences in demographic and pre-treatment characteristics of patients. A, gender. B, age. C, VAS score. D, SNOT-22 score. E, nasal NO concentration. F, fold induction of iNOS. XNI, xylitol nasal irrigation. SNI, saline nasal irrigation. The values shown were expressed as means ± SEMs. n.s., not significant.

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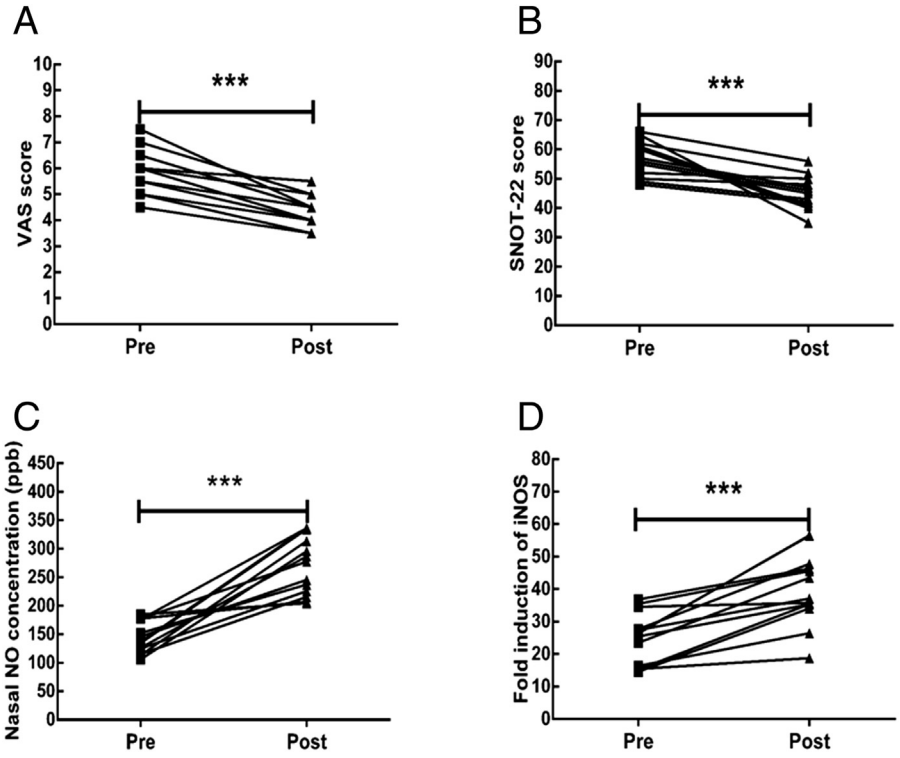


**Fig. 4.** Clinical improvements and changes of nasal NO and iNOS mRNA in the right maxillary sinus after XNI treatment. A, VAS score. B, SNOT-22 score. C, nasal NO concentration. D, fold induction of iNOS. Pre, pre-treatment. Post, post-treatment. The values shown were expressed as means ± SEMs. ***$p < 0.001$.

in the sinuses. As a result, these cells expressed more iNOS mRNA in order to improve innate defense system. Consequently, a large amount of NO was produced from these epithelial cells to prevent the sinus inflammation.

These findings clearly show that xylitol has a definite efficacy on CRS although this study has some limitations such as a small number of patients, a short duration and the absence of the effect of xylitol on the growth of bacteria cultured from sinuses. Further studies on the

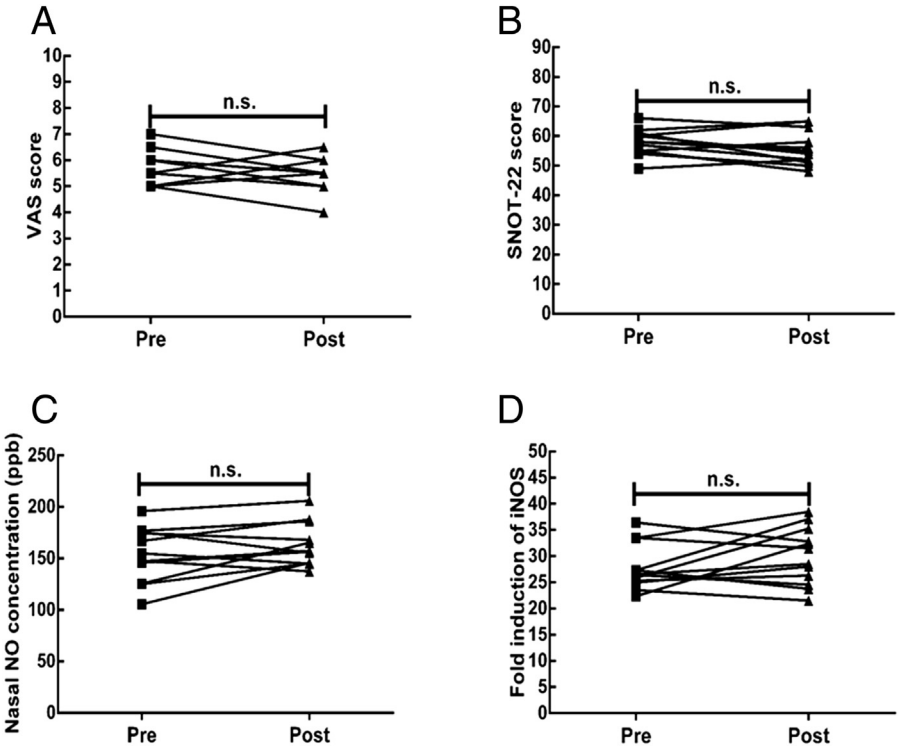


**Fig. 5.** Clinical improvements and changes of nasal NO and iNOS mRNA in the right maxillary sinus after SNI treatment. A, VAS score. B, SNOT-22 score. C, nasal NO concentration. D, fold induction of iNOS. Pre, pre-treatment. Post, post-treatment. The values shown were expressed as means ± SEMs. n.s., not significant.

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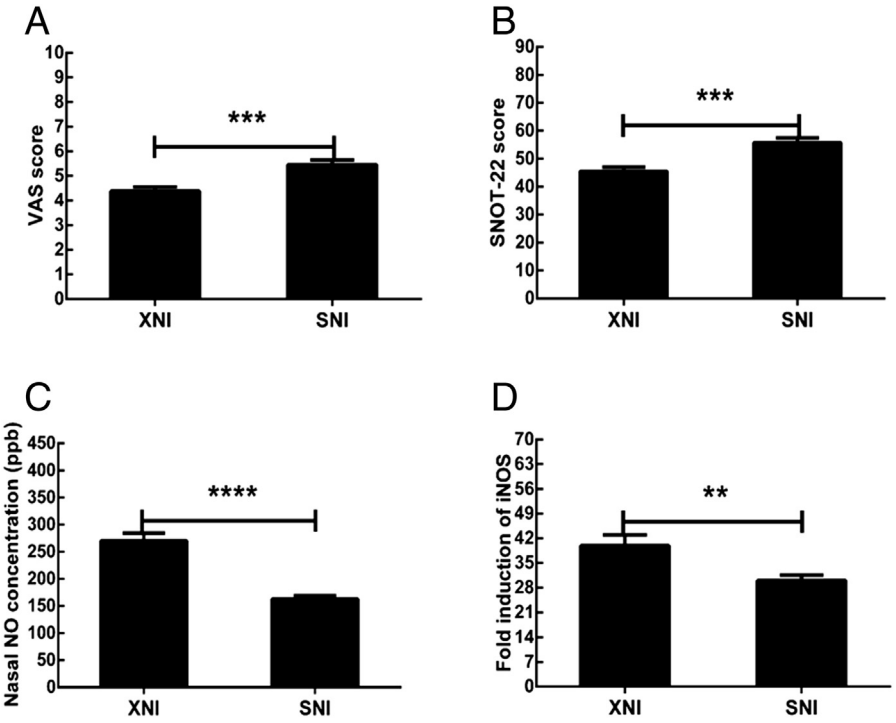


**Fig. 6.** Differences in post-treatment clinical characteristics of patients and changes of nasal NO and iNOS mRNA in the right maxillary sinus between XNI and SNI treatment. A, VAS score. B, SNOT-22 score. C, nasal NO concentration. D, fold induction of iNOS. The values shown were expressed as means ± SEMs. $^{**}p < 0.01$. $^{***}p < 0.001$, $^{****}p < 0.0001$.

underlying mechanisms of the effect of XNI and SNI were needed to be performed. There was another relevant point worth mentioning here. CRS can be divided into two phenotypes dependent on the presence of nasal polyps: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [20]. Based on a previous study, the nasal NO concentration appeared to be dependent on both the allergic status and the degree of obstruction of the paranasal sinuses under the condition of CRS including CRSwNP and CRSsNP [27]. However, patients were excluded if they had a history of allergic rhinitis in this present study. In addition, all patients included in the study undergone bilateral functional endoscopic sinus surgery. That is to say, the obstruction of paranasal sinuses might not be taken into account. Therefore, patients with CRSwNP or CRSsNP would not affect the relevant results.

## 5. Conclusion

In conclusion, this study indicates that XNI improves the scores of VAS and SNOT-22, and also increases the contents of nasal NO and iNOS mRNA in maxillary sinus. However, there are no statistical differences in the above assessments after SNI treatment. XNI results in greater improvement of symptoms of CRS and greater enhancement of nasal NO and iNOS mRNA in maxillary sinus as compared to SNI.

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## Disclosures

The authors have no financial conflicts of interest.

## References

[1] Shashy RG, Moore EJ, Weaver A. Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Arch Otolaryngol Head Neck Surg 2004;130:320–3.
[2] Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA(2)LEN study. Allergy 2011;66:1216–23.
[3] Pynnonen MA, Mukerji SS, Kim HM, et al. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. Arch Otolaryngol Head Neck Surg 2007;133:1115–20.
[4] Goldman MJ, Anderson GM, Stolzenberg ED, et al. Human beta-defensin-1 is a salt-sensitive antibiotic in lung that is inactivated in cystic fibrosis. Cell 1997;88:553–60.
[5] Durairaj L, Launspach J, Watt JL, et al. Safety assessment of inhaled xylitol in mice and healthy volunteers. Respir Res 2004;5:13.
[6] Miyasawa-Hori H, Aizawa S, Takahashi N. Difference in the xylitol sensitivity of acid production among *Streptococcus mutans* strains and the biochemical mechanism. Oral Microbiol Immunol 2006;21:201–5.
[7] Weissman JD, Fernandez F, Hwang PH. Xylitol nasal irrigation in the management of chronic rhinosinusitis: a pilot study. Laryngoscope 2011;121:2468–72.
[8] Djupesland PG, Chatkin JM, Qian W, et al. Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. Am J Otolaryngol 2001;22:19–32.
[9] Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. Acta Otolaryngol 1997;117:113–7.
[10] Lundberg J, Rinder J, Weitzberg E, et al. Nasally exhaled nitric oxide originates mainly in the paranasal sinuses. Acta Physiol Scand 1994;152:431–2.
[11] Lundberg J, Farkas-Szallasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. Nat Med 1995;1:370–3.
[12] Kawamoto H, Takumida M, Takeno S, et al. Localization of nitric oxide synthase in human nasal mucosa with nasal allergy. Acta Otolaryngol Suppl 1998;539:65–70.
[13] Ferreira AS, de Souza MA, Barbosa NR, et al. Leishmania amazonensis: xylitol as inhibitor of macrophage infection and stimulator of macrophage nitric oxide production. Exp Parasitol 2008;119:74–9.
[14] Gaston B, Drazen JM, Loscalzo J, et al. The biology of nitrogen oxides in the airways. Am J Respir Crit Care Med 1994;149:538–51.
[15] Banks CA, Schlosser RJ, Wang EW, et al. Macrophage infiltrate is elevated in CRSwNP sinonasal tissue regardless of atopic status. Otolaryngol Head Neck Surg 2014;151:215–20.
[16] Zabner J, Seiler MP, Launspach JL, et al. The osmolyte xylitol reduces the salt concentration of airway surface liquid and may enhance bacterial killing. Proc Natl Acad Sci U S A 2000;97:11614–9.
[17] Sakallioğlu Ö, Güvenç IA, Cingi C. Xylitol and its usage in ENT practice. J Laryngol Otol 2014;128:580–5.
[18] Kontiokari T, Uhari M, Koskela M. Effect of xylitol on growth of nasopharyngeal bacteria in vitro. Antimicrob Agents Chemother 1995;39:1820–3.
[19] Kontiokari T, Uhari M, Koskela M. Antiadhesive effects of xylitol on otopathogenic bacteria. J Antimicrob Chemother 1998;41:563–5.

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[20] Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 2012;23:1–298 (3 p preceding table of contents).
[21] Katsuyama M, Ichikawa H, Ogawa S, et al. A novel method to control the balance of skin microflora. Part 1. Attack on biofilm of *Staphylococcus aureus* without antibiotics. J Dermatol Sci 2005;38:197–205.
[22] Katsuyama M, Kobayashi Y, Ichikawa H, et al. A novel method to control the balance of skin microflora part 2. A study to assess the effect of a cream containing farnesol and xylitol on atopic dry skin. J Dermatol Sci 2005;38:207–13.
[23] Brown CL, Graham SC, Cable BB, et al. Xylitol enhances bacterial killing in the rabbit maxillary sinus. Laryngoscope 2004;114:2021–4.
[24] Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol 2000;257:537–41.
[25] Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. J Otol HNS 2007;137:815–21.
[26] Jain B, Rubinstein I, Robbins RA, et al. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. Biochem Biophys Res Commun 1993;191:83–8.
[27] Arnal JF, Flores P, Rami J, et al. Nasal nitric oxide concentration in paranasal sinus inflammatory diseases. Eur Respir J 1999;13:307–12.

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